

Selective hydrogenation and transfer hydrogenation reactions

Dissertation

zur Erlangung des akademischen Grades

doctor rerum naturalium (Dr. rer. nat.)

der Mathematisch-Naturwissenschaftlichen Fakultät

der Universität Rostock

angefertigt am Leibniz-Institut für Katalyse e.V.

an der Universität Rostock

im Forschungsbereich

von Prof. Dr. Johanes Gerardus de Vries

“Catalysis with renewables and platform chemicals”

vorgelegt von

Ronald Alvaro Farrar Tobar

M.Sc. Universitat de Barcelona

geb. am. 14.05.1985 in Dénia (Alicante, Spanien)

Rostock, November, 2018

Gutachter:

Prof. Dr. Johannes Gerardus de Vries.
Leibniz-Institut für Katalyse e. V. An der Universität Rostock.
Albert-Einstein-Str. 29a, 18059 Rostock, Germany.

Gutachter:

Prof. Dr. Carmen Claver.
Universitat Rovira I Virgili. / Centre for Chemical Technology of Catalonia (CTQC).
Marcel·li Domingo s/n 43007 Tarragona, Spain.

Jahr der Einreichung: 2018.

Jahr der Verteidigung: 2019.

Wir reiten in die Kreuz und Quer
Nach Freuden und Geschäften;
Doch immer kläfft es hinterher
Und bellt aus allen Kräften.
So will der Spitz aus unserm Stall
Uns immerfort begleiten,
Und seines Bellens lauter Schall
Beweist nur, daß wir reiten.

Kläffer.

Johann Wolfgang von Goethe

οστις γαρ εχει δοθησεται αυτω και περισσευθησεται οστις δε ουκ εχει
και ο εχει αρθησεται απ αυτου

Textus Receptus. KATA MATΘΑΙΟ (13:12)

Acknowledgements

This thesis represents for me something very deep, a very important step forward in my development as a scientist and more also as professional chemist. Taking this step was a rewarding struggle which has been time well spent. At this point is very important for me to share my gratitude with some people who in different ways have made it possible for me to have spent time here in Leibniz Institute for catalysis. First and foremost, I would like to thank to Prof. Dr. Johannes Geraldus de Vries for accepting me from the very first moment and giving to me this priceless opportunity to enrich both my career and personal development in an incomparable, professional and world-wide reputed institution that LIKAT is. It is setting a before and after in my life. Also, highly important mention is deserved for Dr. Sandra Hinze as the group leader for trusting on my potential and showing to me that different approaches are possible. Unavoidable mention is required for Dr. Sergey Tin as group leader for his patience; it contributed a lot and represented a unique support. Special thankfulness should be expressed for all my colleagues in the group of “*Catalysis with Renewables & Platform Chemicals*” during the time that I was there, because their level of knowledge, attitude and desires created such a unique international and challenging environment which made of me fertile earth for growing competence, skills, patience and resilience. It was my pleasure to meet them. In addition I want to thank Professor Dr. Haijun Jiao and his group with especial mention to Zhihong Wei for their careful computational work. Also to Dr. Wohlrab and his group with special mention to Dominik Seeburg for sharing with me such a unique project that Rh single atom is. I would like to give thanks to all single people who work hard and honestly in LIKAT to maintain the high professional activity making my experience much more enriching. A complete list of names would take tens of pages, you know who you are. More concretely, I would like to thank all analytical department for their dedicated job. On the other hand, I also want to thank the state of Mecklenburg-Vorpommern for funding. Finally, a very special mention is deserved for those people who were there from the very first steps 10 years ago, as student first and as researcher later. These people are in one side, some teachers in the University of Barcelona like Professor Dr. Pere Romea and Prof. Dr. Antoni Riera i Escalè and in the other side, like it could not be otherwise, all my beloved family. The existence of all members of my family gives meaning to life. I want specially thank to my mother Maria Inés Tobar Burgos for supporting me and pushing me against the difficulties, without her, none of this would have been possible.

Abstract

Allylic alcohols are very versatile compounds which are used in a large variety of industrial processes. Transfer hydrogenation of α,β -unsaturated carbonyl compounds is a very appealing approach to obtain allylic alcohols. It avoids the use of stoichiometric and hazardous reagents such as NaBH_4 or LiAlH_4 . Furthermore, compared to classical catalytic hydrogenations, these reactions do not require high-pressure equipment. Thus, protocols for transfer hydrogenation are cheaper and safer. One of the major problems in the reduction of unsaturated carbonyl compounds is to achieve high chemo-selectivity. Free energy barriers for the reduction of carbonyl compounds and for the reduction of conjugated carbon-carbon double bonds are often very close in value. For that reason, mixtures of products as well as fully reduced products are often obtained making the scope of many catalysts limited. Herein we review the literature on selective transfer hydrogenation of α,β -unsaturated carbonyl compounds to the allylic alcohols using soluble transition metal complexes as catalysts and explore new systems bearing new features like using EtOH as hydrogen donor allowing in the future for new possibilities in renewable chemistry. Ruthenium is the most employed metal in the field of transfer hydrogenation followed by iridium. In addition, some examples using complexes based on other transition metals including some 1st row transition metals have recently emerged. This is a rapidly growing field. In this work several catalysts are explored in order to find the one which is capable to perform the selective reduction of α,β -unsaturated carbonyl compounds to allylic alcohols using EtOH as a hydrogen source. Best results were obtained with the ruthenium PNP pincer complex Ru-MACHOTM-BH. Afterwards, and with a clear idea of potentially promising homogeneous catalysts for transfer hydrogenation, we examined the reduction of ester functionalities to the alcohols using a TH process. Here the iron PNP pincer complex Fe-MACHO-BH gave very good results. This led to the possibility of new protocols for renewable chemistry and plastic recycling. In the final part of this thesis, in the context of the new emerging field of catalysis like supported single atoms, the research group became interested in exploring new possibilities for achieving high selectivities in different chemical transformations using supported Rh single atoms on Al_2O_3 with especial emphasis on the reduction of aliphatic compounds bearing differently substituted olefins. This showed new interesting features for optimizing the metal loading in supported catalysts while obtaining a very high selectivity. Selective reduction of Limonene was performed and compared with other catalysts in literature showing its good potential for this type of reactions.

Table of Contents

Acknowledgements	I
Abstract	III
Table of Contents	v
List of abbreviations.....	VII
1. Preface.....	1
2. Transfer-hydrogenation of α,β -unsaturated carbonyl compounds	3
2.1 General introduction. State of the art	3
2.1.1. Ruthenium catalysts	5
2.1.2. Iridium catalysts	15
2.1.3. Iron & other less common metals as catalysts.....	19
2.1.4. Meerwein-Ponndorf-Verley reactions	25
2.2. Chapter 1. Selective base-free transfer hydrogenation of α,β -unsaturated carbonyl compounds using EtOH or iPrOH as Hydrogen source.	27
2.2.1. Introduction	27
2.2.2. Objectives.....	27
2.2.3. Results and discussion.....	28
2.2.4. Conclusions and further prospects	39
2.3. Chapter 2. Base-free Fe catalysed transfer hydrogenation of esters compounds using EtOH as H ₂ source.....	41
2.3.1. Introduction. State of the art.....	41
2.3.2. Objectives.....	42
2.3.3. Results and discussion.....	42
2.3.4. Conclusions and further prospects	51
3. Chapter 3. Exploration of Rh single atom catalysis for new chemical transformations.....	53
3.1. Introduction	53
3.1.1. Single atom catalysts (SAC)	53
3.1.2. State of the art in Rh single site catalysts	54
3.2. Objectives.....	55
3.3. Results and discussion.....	56
3.3.1. Synthesis and characterization	56
3.3.2. Optimization conditions	57
3.3.3. Reactivity comparison.....	62
3.4. Conclusions and Further prospects	67

Table of contents

4. Summary	69
5. Experimental part	71
5.1. General considerations	71
5.2. Chapter 1	72
5.2.1. Experimental procedures	72
5.2.2. Analytical data	73
5.3. Chapter 2	78
5.3.1. Experimental procedures	78
5.3.2. Analytical data	80
5.4. Chapter 3	84
5.4.1. Experimental procedures	84
5.4.2. Analytical data	85
6. References	87
7. Miscellaneous	94
7.1. Curriculum Vitae	94
7.2. Selbstständigkeitserklärung	96

List of abbreviations

ATH	Asymmetric transfer hydrogenation	HAADF	High-angle annular dark-field imaging
ADSMC	Atomically dispersed supported metal catalyst	iPr	iso-propyl
bp	Boiling point	ICP	Inductively coupled plasma
COD	Cyclooctadiene	MPV	Meerwein-Ponndorf-Verley
CEOS	Corrected Electron Optical Systems	MTPA	Methoxy- α -trifluoromethylphenylacetic acid
°C	Centigrade	MS	Mass spectroscopy
DMSO	Dimethylsulfoxide	MACHO	Bis(2-di-alkyl/aryl-phosphinoethyl)amino
DSM	Dutch State Mines	MSD	Mass selective detector
DIPEA	<i>N,N</i> -Diisopropylethylamine	NP	Nanoparticle
DOSY	Diffusion Ordered Spectroscopy	NHC	Arduengo-type N-heterocyclic carbene
EtOH	Ethanol	OES	Optical Emission Spectrometer
ee	Enantiomeric excess	pH	Minus logarithm of hydrogen chemical potential
ESI	Electrospray ionization	PTA	Phosphotungstic acid
GLC	Gas liquid chromatography	rt	Room temperature
GC	Gas chromatography	RTMS	Remote Traffic Microwave Sensor
HDMA	Hexane-1,6-diamine	SSHC	Single site heterogeneous catalysts
HPLC	High pressure liquid chromatography	SAC	Single atom catalyst
H-NMR	Proton nuclear magnetic resonance	SIHC	Site-Isolated Heterogeneous Catalysts
HSMSC	Heterogeneous single-metal site catalyst	SpiroPAP	Spiro-pyridine-aminophospine

List of abbreviations

SPHOS	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl	STEM	Scanning transmission electron microscope
SPR16	Slurry phase reactor 16	TS	Transition state
TLC	Thin layer chromatography	TM	Trade mark
TH	Transfer hydrogenation	TPR	Temperature program reduction
TsDPEN	N-tosylated 1,2-Diphenyl-1,2-ethylenediamine	TEM	Transmission electron microscopy
TOF	Turn over frequency	XPS	X-ray photoelectron spectroscopy
tzNHC	1,2,3-triazol-5-ylidene	XRD	Powder X-ray diffraction
Tf	Triflate		

1. Preface. Bio-Based EtOH as raw material for crotyl alcohol, a new platform chemical.

Nowadays we are witnessing a change in the way resources are obtained. Energy and a large variety of chemicals used to be obtained from fossil fuels. However, depletion of these resources is imminent.^[1] Thus, new strategies need to be developed in order to supply renewable resources to cover human demands. One promising alternative to fossil fuels is biomass. A huge amount of biomass is available in different forms.^[2] It is already possible to obtain energy and different platform chemicals, which are needed to produce bulk chemicals for materials, medicines and many other products, from biomass. Here we will focus on obtaining chemicals from biomass. A large amount of research is already being performed to upgrade the value of biomass by transforming it into profitable platform chemicals and bulk chemicals (Figure 1). From sugars, present in lignocellulose, aliphatic platform chemicals can be obtained. From lignin, aromatic platform chemicals; from triglycerides, useful building blocks for polymers.

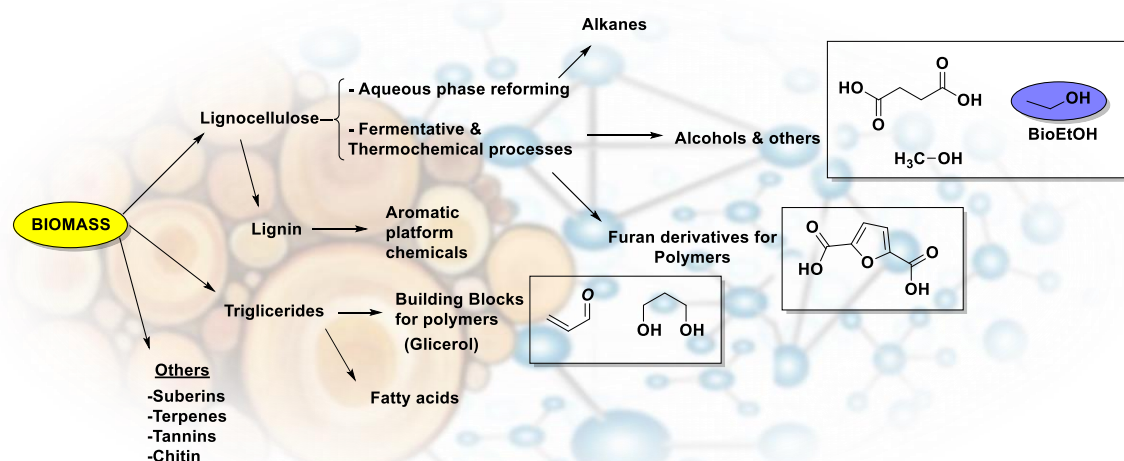


Figure 1. Main pathways for renewable platform chemicals obtentions in Biomass upgrading and some examples of final products.

Other sources like suberin, tannins, terpenes and chitin may also be used. The next step in biomass valorisation would be then, the transformation of these obtained bulk/platform chemicals in other more interesting valuable chemicals. To achieve this goal, thermochemical processes, homogeneous catalysis, biomass gasification for synthesis gas production (CO_2 and H_2) and fermentative production are the fields where advances are being developed. The production of furan-2,5-dicarboxylic acid for polymers, the large scale production of MeOH and alkanes^[3] and the fermentation of sugar to give succinic^[4] and EtOH^[5] are examples of this. Therefore, bioethanol is a renewable resource and is already being produced on a very large scale in a lignocellulose based plant.^[6] Our interest in bioethanol derives from its value as a platform chemical to afford crotyl aldehyde (Scheme 1). Crotyl alcohol has the potential to become a high value platform chemical due to its versatility as a raw material. (Figure 2). Crotyl alcohol could be used as a platform chemical to obtain many different interesting bulk chemicals such as butyraldehyde, used as a raw material for plasticisers and many other like 1,4-butanediol, caprolactam or hexamethyl-1,6-endiamine among others. Crotyl alcohol could be

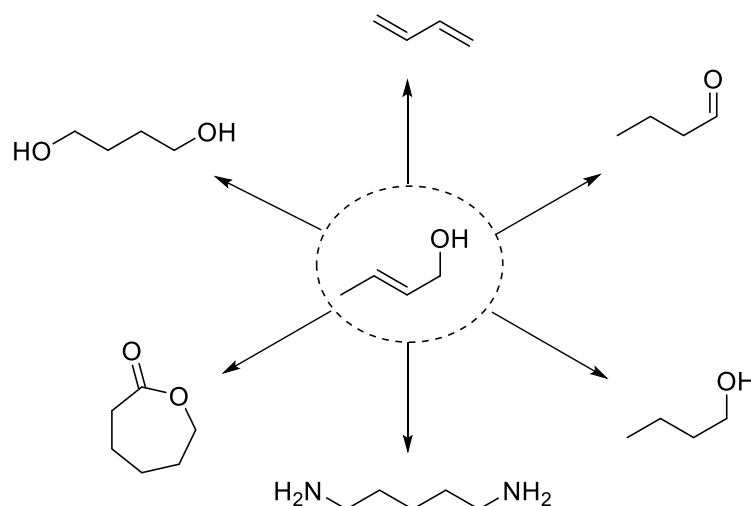
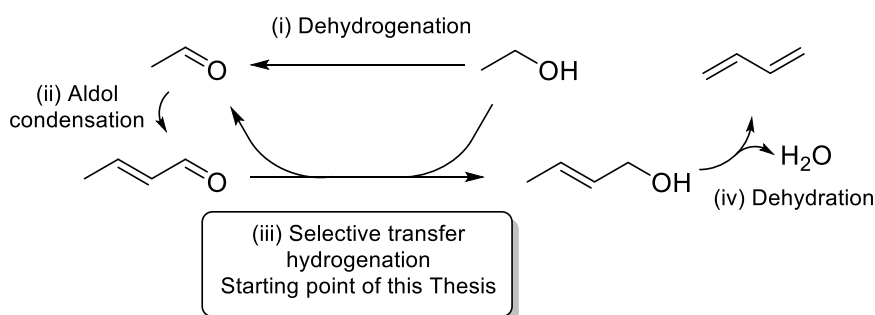


Figure 2. Crotyl alcohol as platform chemical. Possible transformations of crotyl alcohol into useful products.

considered as a liquid form of 1,3-butadiene, but it is much easier to transport and handle. 1,3-butadiene has a high economic value as a bulk chemical. Indeed, the production almost reached 13×10^6 tonnes/year in 2017.^[7] This bulk chemical is used to produce different types of rubbers. A small amount of this product is also used in hexane-1,6-diamine (HDMA) production which is an important intermediate in the nylon production. To produce butadiene from ethanol there already exist 2 processes. The first one, the Lebedev process which uses ZnAl_2O_3 or MgO/SiO_2 as catalyst. And the second one, Ostromislensky which uses Ta_2O_5 .^[8] These processes were widely used in World War II to produce butadiene for rubbers. However, after World War II the oil became available again and butadiene was produced by cracking. The main shortcoming of these processes are the low yields that were obtained which never get over 60%. The most accepted mechanism for this transformation is the one shown in the Scheme 1.



Scheme 1. Most accepted mechanism for the synthesis of 1,3-butadiene from EtOH.

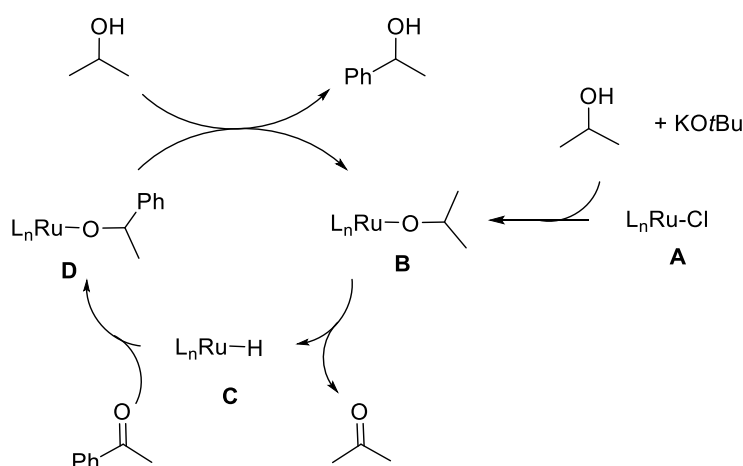
The approach towards a process for butadiene from ethanol in our group focuses on optimizing the distinct steps depicted in scheme 1 and recombine them in a flow process to produce crotyl alcohol. Thus, the starting point of this thesis lies on the exploration of the transfer hydrogenation of crotonaldehyde and generally α,β -unsaturated carbonyl compounds. The use of EtOH as hydrogen donor is highly preferred because the side product acetaldehyde could possibly be reintroduced as starting material in the production of crotonaldehyde.

2. Transfer-hydrogenation of α,β -unsaturated carbonyl compounds

2.1 General introduction. State of the art

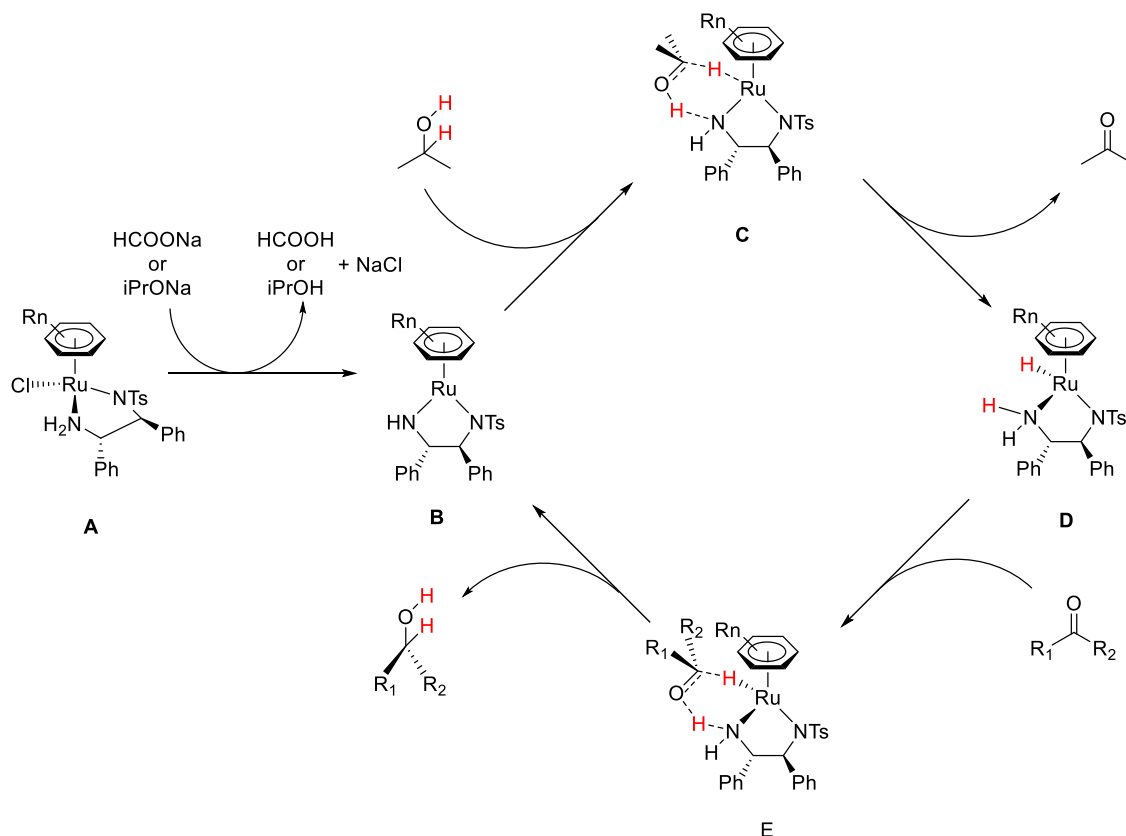
Transfer hydrogenation allows the reduction of a large variety of compounds, such as aldehydes, ketones, imines, alkenes, alkynes, nitro-compounds, nitriles and esters in a simple and safe manner.^[9] In particular the reduction of ketones and imines has also been performed enantioselectively using chiral transition metal-based catalysts. Using transfer hydrogenation, the use of potentially explosive hydrogen as well as the use of high pressure equipment can be avoided. The method conforms to a number of the green chemistry principles such as: less hazardous chemical synthesis, use of an innocuous solvent, use of catalysis and inherently safer chemistry. The most common hydrogen sources are iPrOH and HCOOH. To a lesser extent other alcohols such as potentially renewable EtOH and cyclohexanol have also been studied. Also, other sources like ammonia borane or hydrazine were reported as potential sources of hydrogen for transfer hydrogenation. Depending on the hydrogen source employed, different by-products will be obtained. When iPrOH is used, acetone is obtained; when EtOH is used, acetaldehyde is the by-product which reacts further with another equivalent of ethanol; dehydrogenation of the formed hemiacetal gives ethyl acetate.^[10] In case HCOOH is the source of hydrogen, CO₂ is produced.^[11] With the latter two reductants, the reaction is irreversible allowing 100% conversion of the substrate. Using isopropanol, the transfer hydrogenation is an equilibrium reaction necessitating the use of a large excess of iPrOH to achieve conversions in excess of 95%. Once the catalyst is in its active state, it can reduce the substrate to the desired product via different pathways. There are 3 main reaction mechanisms described for these reactions:^[12]

- a) The inner sphere mechanism (Scheme1). In this mechanism the metal halide complex **A** reacts with isopropoxide to form the isopropoxy complex **B**, which undergoes beta-hydride elimination to form the metal hydride complex **C**. Insertion of the carbonyl compound into the metal hydride gives the new metal alkoxide complex **D**, which undergoes exchange with isopropanol to reform the metal isopropoxide complex.



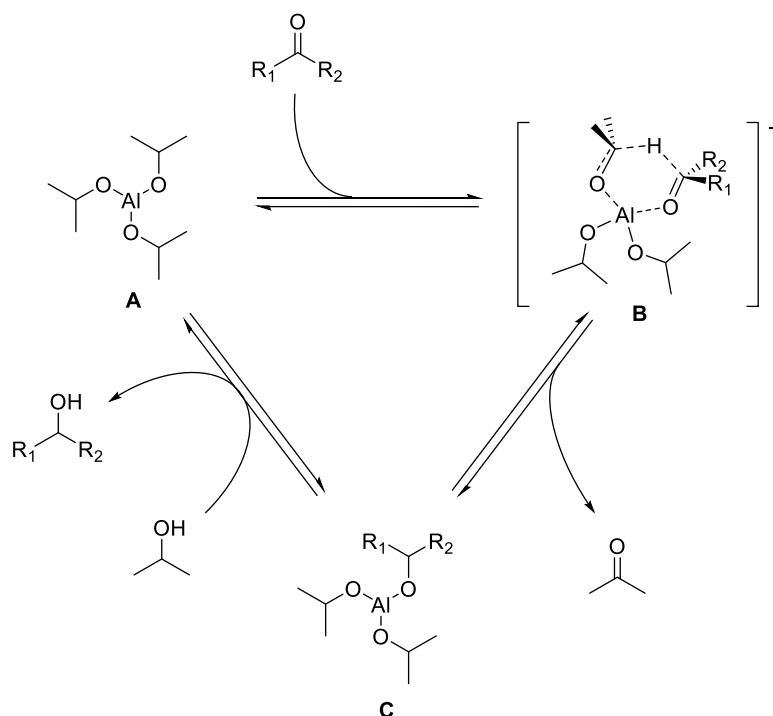
Scheme 1. Inner sphere mechanism

- b) The outer sphere mechanism (Noyori-Morris, Scheme 2) whereby the hydride of the metal is transferred directly to the substrate and the proton is either transferred from a ligated amino or hydroxy group in the ligand as in the Noyori mechanism (Scheme 2) or from the solvent as exemplified in the Dub and Gordon mechanism.^[13] After that, the catalyst is ready to dehydrogenate the hydrogen source (isopropanol in this case) to furnish the active hydride-NH form of the catalyst again.



Scheme 1. Noyori-Morris outer sphere mechanism.

- c) The Meerwein-Verley-Ponndorf reaction follows a completely different mechanism.^[14] (Scheme 3) In this case, a carbonyl compound is coordinated to a strong Lewis acid metal complex like $\text{Al}(\text{iPrO})_3$ forming a tetrahedral intermediate **B**. Then, a direct hydride transfer occurs from one of the alkoxide groups to the carbonyl via a 6-membered transition state. After the release of one molecule of acetone, a new tridentate complex **C** is formed. Finally, the desired product is released by alkoxide exchange with another iPrOH molecule to form $\text{Al}(\text{iPrO})_3$, closing the cycle. All steps in this mechanism are equilibria. Thus, the conversion is governed by the thermodynamic characteristics of the species involved and by the excess of reductant.



Scheme 2. Meerwein-Ponndorf-Verley mechanism

Due to the versatility of the transfer hydrogenation reaction, its application in both academia and industry is paramount. One type of substrate which is particularly challenging to be reduced via transfer hydrogenation are the α,β -unsaturated carbonyl compounds, and more specifically the carbonyl bond in α,β -unsaturated aldehydes and ketones. The difference in activation energy between the reduction of the C=C conjugated double bond compared to the C=O bond is relatively small.^[15] For that reason, mixtures of ketones, allylic alcohols and over reduced products may be obtained. However, in some cases selectivity towards carbonyl compounds can be achieved by kinetic control of the reactions. Recently, Dub and Gordon rationalized the C=O,C=C selectivity obtained in some systems as a consequence of the C=O reduction within the outer sphere of the metal centre caused by non-innocent ligands.^[13c] Allylic alcohols are very important molecules in the chemical industry as they are used as intermediates in the synthesis of a large variety of commercial products. Furthermore, glycerol monomers, such as 1,4-butanediol or allyl carbonates are prepared from allyl alcohol.^[16] In the fragrance industry, allylic alcohols are important intermediates.^[17] In addition, allylic alcohols also represent key intermediates in organic synthesis. For example, for hydroformylations^[18] or β -arylations.^[19] Classic hydrogenation of this type of substrates using hydrogen gas was briefly reviewed in the context of the reduction of citral.^[20] In this introduction we cover mainly examples of homogeneous systems reported within the last 30 years and only a few relevant older ones.

2.1.1. Ruthenium catalysts

Ruthenium based complexes are by far the most reported catalysts in the transfer hydrogenation of α,β -unsaturated carbonyl compounds.

2.1.1.1. Chiral metal catalysts

2.1.1.1.1. Using iPrOH as hydrogen donor ^[21]

Back in the nineties, Ryoji Noyori and co-workers developed ruthenium catalysts that were prepared from the reaction between $[\text{Ru}(\text{Arene})\text{Cl}_2]_2$ and tosylated 1,2-diaryl-ethylenediamines or 1,2-diaryl-aminoethanol as chiral ligands for the asymmetric transfer hydrogenation (ATH) of α,β -acetylenic ketones (Fig. 1).^[21a] They used iPrOH as hydrogen source and the catalysis was successful using 0.5 mol% catalyst loading at 28 °C, affording the desired unsaturated alcohols with very high enantio-selectivities and yields (Table 1, entries 1-8). More than a decade after, Adolfsson's group was examining the use of a combination of the same ruthenium source combined with a hydroxy amide ligand derivatized from L-ananine.^[21b] With these catalysts, more than 10 substituted propargylic ketones were reduced to the corresponding propargylic alcohols in a TH process using iPrOH as hydrogen source in Toluene. High yields and high enantioselectivities in very short reaction times were achieved. For some examples see Table 1 (Entries 9-11). To prove the robustness of the system, scaling up the reaction to 10 mmol with substrate **7a** gave 88% yield of desired product with 97% ee in only 30 min. The following year Adolfsson, Pamies and Diéguez and co-workers reported more bio-based ligands for ruthenium catalysis. They synthesized a modular ligand library of α -amino acid hydroxy amides and thioamides.^[21c] One example of this library is the 2,3-O-isopropylidene- α -D-mannofuranoside derivative **6b** which in combination with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ succeeded in the TH of **7a** to afford the propargylic alcohol with 89% isolated yield and 96% ee (Table 1, entry 12). However, only 34% isolated yield was achieved when benzalacetone was the substrate. The ee was still as high as 95% (Table 2, entry 7). Interestingly, this catalyst also showed high activity for other type of transformations such as a tandem isomerization/asymmetric transfer hydrogenation of racemic allylic alcohols to the saturated alcohols and α -alkylation/asymmetric transfer hydrogenation of acetophenone and 3-acetylpyridine with primary alcohols.

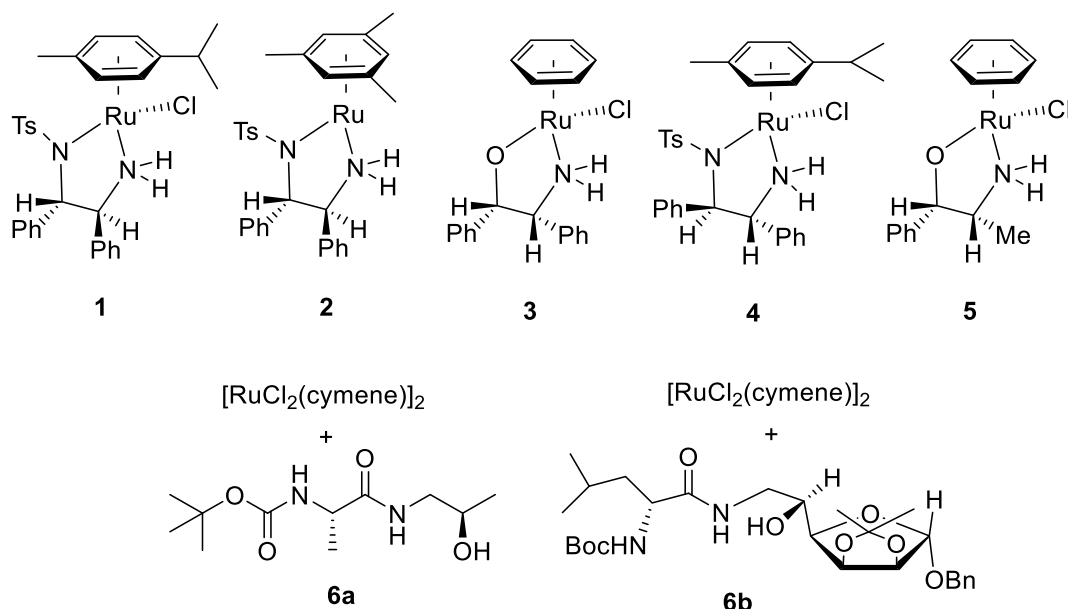
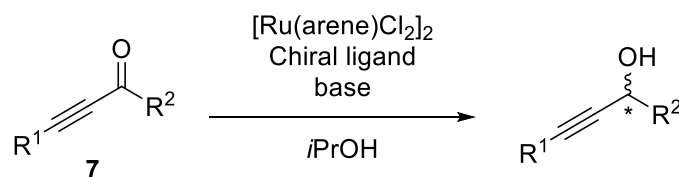


Figure 3. Ruthenium based catalysts for the chiral reduction of α,β -unsaturated carbonyl compounds using iPrOH as hydrogen donor.

Table 1. Enantioselective transfer hydrogenation of α,β -acetylenic ketones to the corresponding chiral alcohols using ruthenium catalysts **1**, **2** and **6a,b** using *i*PrOH as hydrogen source.



7a $R^1 = \text{Ph}$, $R^2 = \text{CH}_3$

7b $R^1 = \text{Ph}$, $R^2 = \text{CH}(\text{CH}_3)_2$

7c $R^1 = \text{Ph}$, $R^2 = c\text{-C}_6\text{H}_{11}$

7d $R^1 = \text{Si}(\text{CH}_3)_3$, $R^2 = \text{CH}_3$

7e $R^1 = \text{Si}(\text{CH}_3)_3$, $R^2 = n\text{-C}_5\text{H}_{11}$

7f $R^1 = \text{Si}(\text{CH}_3)_3$, $R^2 = \text{CH}(\text{CH}_3)_2$

7g $R^1 = \text{Si}(\text{CH}_3)_3$, $R^2 = \text{CH}(\text{CH}_3)\text{CH}(\text{OTBS})\text{CH}(\text{CH}_3)\text{CH}_2\text{OTBS}$

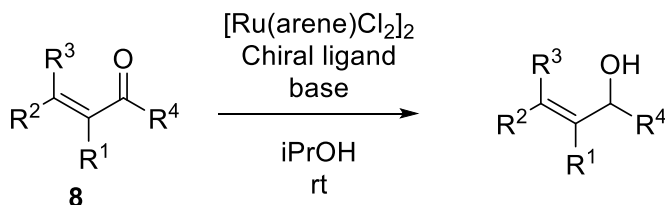
Entry	Cat.	Cat. Loading (Mol%)	Base	Substrate	Temp.	Yield ^a (%)	ee (%)	Time (hours)	Ref.
1	1	0.5	---	7a	28	>99	97 ^b	20	[21a]
2	2	0.5	KOH	7a	28	>99	97 ^b	4	[21a]
3	2	0.5	KOH	7a	28	>99	98 ^b	18	[21a]
4	2	0.5	KOH	7b	28	98	99 ^b	5	[21a]
5	2	0.5	KOH	7c	28	>99	98 ^b	13	[21a]
6	1	0.5	---	7d	28	>99	98 ^b	12	[21a]
7	1	0.5	---	7e	28	98	99 ^b	15	[21a]
8	1	0.5	---	7f	28	99	99 ^b	12	[21a]
9	6a	1	<i>t</i> BuOK	7a	rt	91	97	10	[21b]
10	6a	1	<i>t</i> BuOK	7b	rt	98	99	10	[21b]
11	6a	1	<i>t</i> BuOK	7d	rt	0	---	---	[21b]
12	6b	0.25	<i>t</i> BuOK/LiCl	7a	rt	89	96	10 ^c	[21c]

^aIsolated yield. ^bHPLC analysis using Daicel Chiralcel OD column unless otherwise specified. ^cTime in minutes.

A slightly lower ee was obtained when catalyst **3** was used for the reduction of deuterated cinnamaldehyde as substrate (Table 2 entry 1) compared to TsDPEN ligand base catalysts. Püntener as well as Hawaii Biotech were also working with the same catalysts targeting the reduction of substrate **8b** (Table 2, entries 2, 4).^[21e, 21g] In both cases, very good enantioselectivities in short reaction times were achieved. It is worth to mention that Püntener and Hawaii Biotech observed selectivity towards the more hindered carbonyl group. In addition, Püntener reported the crystal structures of different ruthenium catalysts in this family. However selectivity was slightly lower in all cases. Using Noyori's ruthenium catalyst **1**, the group of Zhaoguo Zhang reduced selectively several α -keto β,γ -unsaturated esters with high yields and moderate enantioselectivities using *i*PrOH as the hydrogen source.^[21h] In this study, in order to achieve the desired selectivity towards the carbonyl moiety, isolating the previously activated catalyst was crucial. With this protocol, 2 heteroaromatic substituted substrates **8c** and **8d** were reduced to the desired unsaturated alcohols with 99% and

96% isolated yields, respectively, in only 1 hour reaction time among other substrates (Table 2, entries 5-6). The observed ee's were up to 65%.

Table 2. Enantioselective transfer hydrogenation of α,β -unsaturated ketones by ruthenium catalysts in *i*PrOH.



8a $R^1 = H, R^2 = Ph, R^3 = H, R^4 = D$

8b [Cycle] $R^1 = Me, R^2 = H, [R^3 = COCH_2C(CH_3)_2 = R^4]$ (Ketoisophorone)

8c $R^1 = H, R^2 = 2\text{-furanyl}, R^3 = H, R^4 = COOCH(CH_3)_2$

8d $R^1 = H, R^2 = 2\text{-thiophenyl}, R^3 = H, R^4 = COOCH(CH_3)_2$

8o $R^1 = R^3 = H, R^2 = Ph, R^4 = Me$

Entry	Cat.	Loading (mol%)	Base	Substr.	Yield (%)	ee (%)	Time (hours)	Ref.
1	3	1	<i>t</i> BuOK	8a	97 ^a	72 ^b	0.25	[21d]
2	3	1	NaOH	8b	>99 ^c	97 ^c	0.5	[21e]
3	4 or 1	5	---	7g	76	95	overnight	[21f]
4	5	0.8	NaOH	8b	60	^d	3	[21g]
5	1	1	---	8c	99 ^c	59	1	[21h]
6	1	1	---	8d	96 ^c	65	1	[21h]
7	6b	1	<i>t</i> BuOK/LiCl	8o	34 ^e	95	10 ^f	[21c]

^aDetermined by GLC analysis. ^bDetermined by ¹H-NMR analysis of the corresponding MTPA-ester. ^cConversion and ee determined by CG analysis. ^dProduct identified as *R*-enantiomer without ee determination. ^eIsolated Yield. ^fTime in minutes.

2.1.1.1.2. Using formic acid as hydrogen donor ^[22]

Ru-arene complexes are also active in ATH when HCOOH is used as hydrogen donor. The group of Wills, showed that catalysts **1** and **11** can afford enantioselectivities up to 99% when using HCOOH/Et₃N in the reduction of α,β -acetylenic carbonyl compounds (Table 3, entries 4-6,8-9).^[22a-c, 22e, 22k, 22l] In the same report, higher activity and increased selectivity were described when catalysts were modified by bridging the arene moiety and the diamine ligand forming catalysts **10** and **11a** (Figure 2). This effect was rationalized by a π/CH edge/face directing effect of aryl-substituted substrates. Then, using catalyst loadings between 0.5 mol% and 10 mol%, the desired unsaturated alcohols were obtained with ee values up to 99%. (Table 3, entries 1-3,7,10-12). Wills kept working on rationalizing the enantioselectivity of these Ru TsDPEN complexes. This led to a very recent report on the TH of more challenging aryl/acetylenic ketones.^[22d] The strategy consisted of introducing an electron-donating group on the aryl moiety of the catalyst **11a**, **11b** (Figure 2) combined with the use of aryl/acetyl *ortho*-substituted substrates. This allowed them to play with both electronics and sterics, thus increasing the enantioselectivity. Some examples from the scope are shown in Table 3 (Entries 13-15).

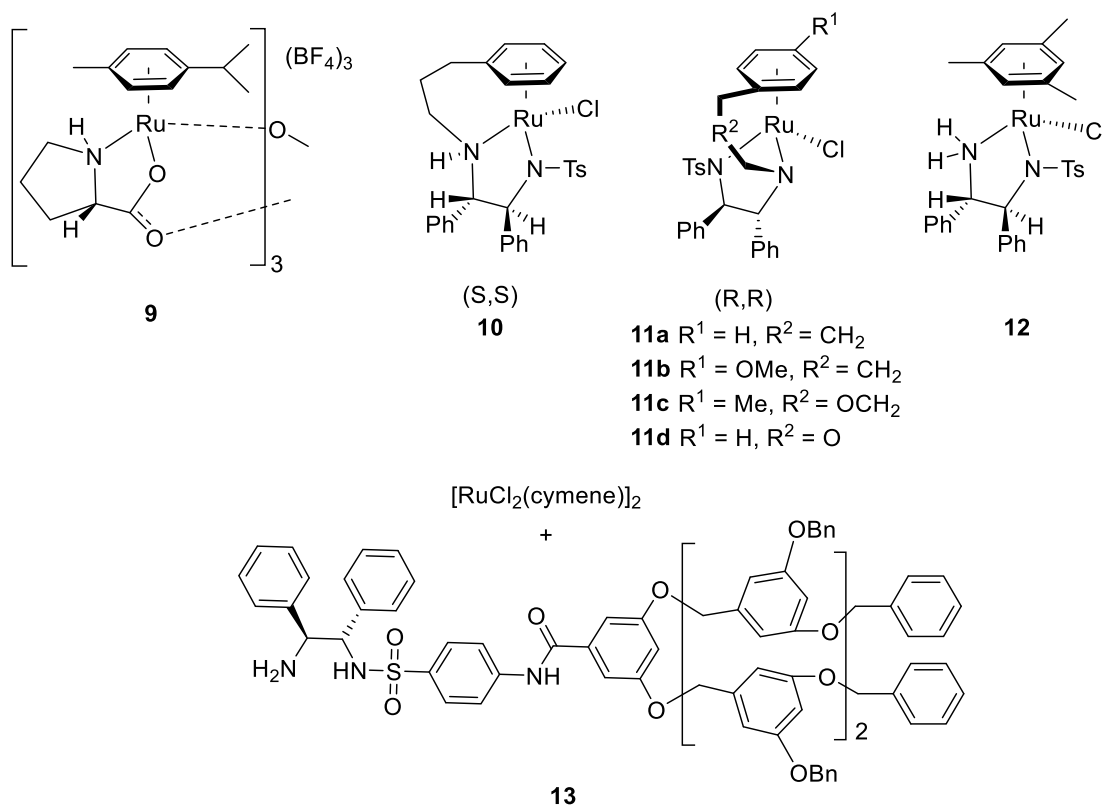
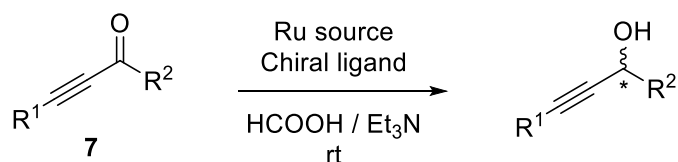


Figure 2. Ruthenium based catalyst for chiral reduction of α,β -unsaturated carbonyl compounds using HCOOH as hydrogen donor.

Table 3. Enantioselective transfer hydrogenation of α,β -acetylenic carbonyl compounds by ruthenium catalysts using HCOOH as hydrogen donor.

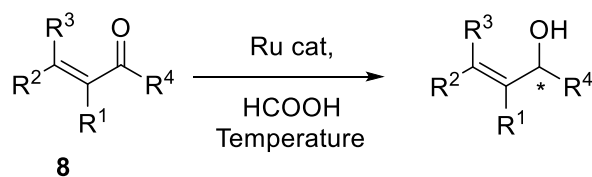


- 7h** $\text{R}^1 = \text{C}\equiv\text{C}-(n\text{-C}_4\text{H}_9), \text{R}^2 = n\text{-C}_3\text{H}_7$
- 7i** $\text{R}^1 = \text{C}\equiv\text{C}-(\text{CH}_2)_4\text{OH}, \text{R}^2 = \text{CH}_3$
- 7j** $\text{R}^1 = \text{C}\equiv\text{C}-(n\text{-C}_4\text{H}_9), \text{R}^2 = \text{CH}_2(\text{C}_6\text{H}_5)$
- 7k** $\text{R}^1 = \text{C}(\text{CH}_3)_2\text{OBn}, \text{R}^2 = (\text{CH}_2)\text{COOCH}_3$
- 7l** $\text{R}^1 = \text{Ph}, \text{R}_2 = \text{CH}(\text{CH}_3)\text{COOCH}_2\text{CH}_3$
- 7m** $\text{R}^1 = \text{C}(\text{CH}_3)_2\text{OBn}, \text{R}^2 = \text{CH}(\text{CH}_3)\text{COOCH}_2\text{CH}_3$
- 7n** $\text{R}^1 = (\text{CH}_2)_2\text{OBn}, \text{R}^2 = (\text{CH}_2)_3\text{COOCH}_3$
- 7o** $\text{R}^1 = \text{Ph}, \text{R}^2 = (\text{CH}_2)_3\text{COCC}(\text{C}_6\text{H}_5)$
- 7p** $\text{R}^1 = \text{C}(\text{CH}_3)_2\text{OBn}, \text{R}^2 = (\text{CH}_2)_3\text{COCCC}(\text{CH}_3)_2\text{OBn}$
- 7q** $\text{R}^1 = \text{Ph}, \text{R}^2 = o\text{-(Cl)Ph}$
- 7r** $\text{R}^1 = \text{Ph}, \text{R}^2 = o\text{-(MeO)Ph}$
- 7s** $\text{R}^1 = \text{Ph}, \text{R}^2 = o\text{-(BnO)Ph}$

Entry	Cat.	Loading. (%mol)	Substrate	Yield ^a (%)	ee (%) ^b	Time (hours)	Ref.
1	10	10	7h	95	98	3	[22a]
2	10	10	7i	96	>90	3	[22a]
3	10	10	7j	92	98	3	[22a]
4	1	10	7h	91	97	3	[22a]
5	1	10	7i	89	>90	3	[22a]
6	1	10	7j	90	97	3	[22a]
7	11a	0.5	7k	99	99	48	[22b, 22c]
8	4	3.34	7l	99	98	48	[22b, 22c]
9	4	3.34	7m	90	99	48	[22b, 22c]
10	11a	0.2	7n	99	99	48	[22b, 22c]
11	11a	0.5	7o	96	>99	48	[22b, 22c]
12	10	0.5	7p	97	>99	48	[22b, 22c]
13	11b	0.1	7q	94	68	40	[22d]
14	11b	0.1	7r	91	59	40	[22d]
15	11b	0.1	7s	93	61	40	[22d]

^aIsolated yields. ^bDetermined by HPLC.

Carmona and co-workers synthesized a trimeric ruthenium cluster (Figure 2, **9**) for the transfer hydrogenation of cinnamaldehyde (**8e**) and citral (**8f**) (Table 4, entries 1-2).^[22f] Substituting the arene moiety in Noyori's catalyst **1** by mesitylene gave catalyst **12** (Figure 2).^[22g] Use of 0.5 mol% of **12** in the presence of Et₃N was sufficient for the reduction of several α,β -unsaturated carbonyl compounds to the corresponding allylic alcohols with excellent enantioselectivities (Table 4, entries 4-6). The group of Ying Chun-Chen designed and synthesized Fréchet-type core-functionalized chiral diamine-based dendritic ligands which they combined with [Ru(*p*-cymene)Cl₂]₂ (**13**).^[22h] By modifying this type of ligands they were able to control the solubility, which allowed them to recycle the catalyst several times. In addition, three benzalacetone derivatized substrates were reduced to the corresponding allylic alcohols in high isolated yields (Table 4, entries 7-9). The enantioselectivity was comparable with the one obtained with the monomeric counterpart. Ikarya, one of the pioneers of asymmetric transfer hydrogenation, and his co-workers developed a new generation of oxo-tethered Ruthenium amido complexes (Figure 2, **11c**).^[22i] These new generation presented very high activity allowing to work at catalyst loadings down to 0.0025 mol% giving high yields and high enantioselectivities when aromatic ketones were used as substrates under TH conditions. Also, the cyclic α,β -unsaturated ketone Seudonone **8m** was reduced at 60 °C in 7 hours to the corresponding enantio enriched unsaturated alcohol using 0.5 mol% catalyst loading with 94% yield and 96% ee (Table 4, entry 10). In the same year, Wills and his team were also modifying these tethered ruthenium complexes by introducing an ether group in the aliphatic bridge (Figure 2, **11d**).^[22j] In spite of the fact that several aromatic ketones were successfully reduced with high yields and good enantioselectivities, 13 days were necessary for the reduction of 1-acetyl-cyclohexene to the corresponding allylic alcohol (Table 4, entry 11). This result was hypothesized to be a consequence of the interaction between the ketone moiety from the substrate and the ether function of the catalyst.

Table 4. Enantioselective transfer hydrogenation of α,β -unsaturated carbonyl compounds by ruthenium catalysts using HCOOH as hydrogen donor.**8b** [Cycle] $R^1 = \text{Me}$, $R^2 = \text{H}$, [$R^3 = \text{COCH}_2\text{C}(\text{CH}_3)_2 = R^4$] (Ketoisophorone)**8e** $R^1 = R^3 = R^4 = \text{H}$, $R^2 = \text{Ph}$ **8f** $R^1 = R^4 = \text{H}$, $R^2 = (\text{CH}_2)_2\text{CH}=\text{C}(\text{CH}_3)_2$, $R^3 = \text{Me}$ **8g** $R^1 = R^3 = \text{H}$, $R^2 = \text{Ph}$, $R^4 = \text{CH}(\text{OCH}_3)\text{COOCH}_3$ **8h** $R^1 = R^3 = \text{H}$, $R^2 = p\text{-MePh}$, $R^4 = \text{CH}(\text{OCH}_3)\text{COOCH}_3$ **8i** $R^1 = R^3 = \text{H}$, $R^2 = m\text{-MePh}$, $R^4 = \text{CH}(\text{OCH}_3)\text{COOCH}_3$ **8j** $R^1 = R^3 = \text{H}$, $R^2 = \text{thiophenyl}$, $R^4 = \text{CH}(\text{OCH}_3)\text{COOCH}_3$ **8k** $R^1 = \text{H}$, $R^3 = R^4 = \text{Me}$, $R^2 = \text{Ph}$ **8l** $R^1 = \text{H}$, $R^3 = R^4 = \text{Me}$, $R^2 = p\text{-MeOPh}$ **8m** [Cycle] $R^1 = \text{H}$, [$R^3 = (\text{CH}_2)_3 = R^4$], $R^2 = \text{Me}$ (Seudenone)**8n** [Cycle] [$R^1 = (\text{CH}_2)_4 = R^2$], $R^3 = \text{H}$, $R^4 = \text{Me}$

Entry	Cat.	Loading. [mol%]	Base	Temp.(°C)	Substrate	Yield (%)	ee (%)	Time (hours)	Ref.
1	9	0.7	HCOONa	83	8e	41 ^a	---	1	[22f]
2	9	0.7	HCOONa	83	8f	82 ^a	---	1	[22f]
3	12	0.5	Et ₃ N	30	8g	>99 ^b	99 ^c	20	[22g]
4	12	0.5	Et ₃ N	30	8h	>99 ^b	99 ^c	20	[22g]
5	12	0.5	Et ₃ N	30	8i	>99 ^b	99 ^c	20	[22g]
6	12	0.5	Et ₃ N	30	8j	>99 ^b	98 ^c	20	[22g]
7	13	1	Et ₃ N	28	8g	85 ^d	37 ^e	28	[22h]
8	13	1	Et ₃ N	28	8k	91 ^d	75 ^e	45	[22h]
9	13	1	Et ₃ N	28	8l	54 ^d	78 ^e	72	[22h]
10	11c	0.5	Et ₃ N	60	8m	94 ^f	96 ^e	6	[22i]
11	11d	0.5	Et ₃ N	30	8n	99 ^f	71 ^e	13 ^g	[22j]

^aDetermined by GLC ^bDetermined by analysis of the ¹H-NMR of the crude product. ^cDetermined by CSP-SCF.^dIsolated Yield. ^eDetermined on a chiral column. ^fDetermined by GC or ¹H-NMR spectroscopy. ^gTime in days.

2.1.1.2. Non-chiral ruthenium catalysts

2.1.1.2.1. Using iPrOH and other aliphatic alcohols as hydrogen donor ^[23]

The ruthenium complexes reported for the TH of α,β -unsaturated carbonyl compounds using alcohols as hydrogen donors are shown in figure 3.

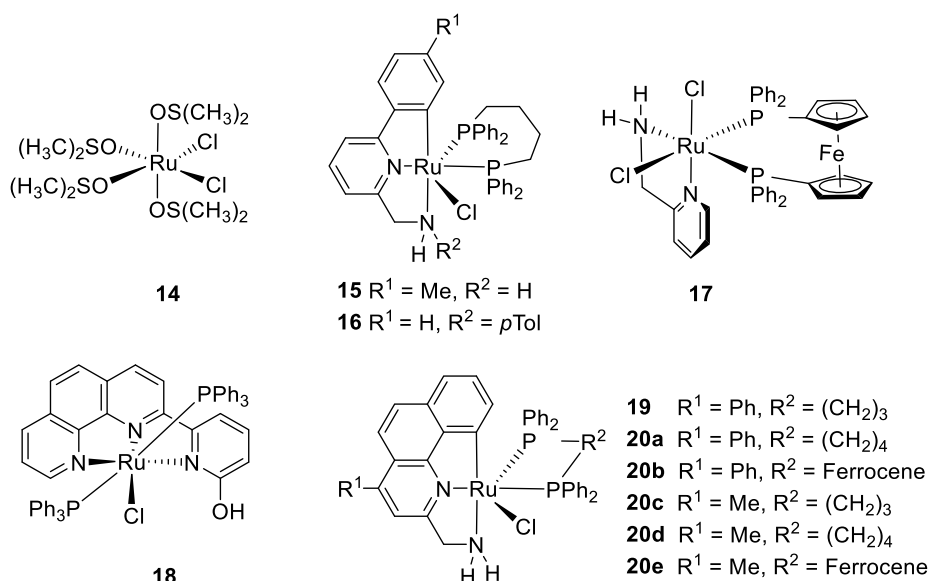
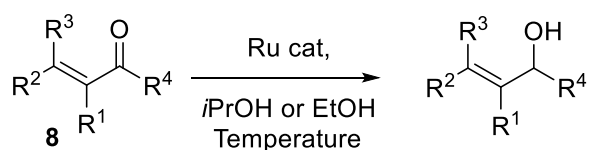


Figure 3. Non-chiral ruthenium catalysts for transfer hydrogenation of α,β -unsaturated carbonyl compounds using alcohols as hydrogen source.

Iyer and co-workers achieved good results in the TH of several α,β -unsaturated carbonyl compounds using a very simple phosphine-free DMSO-Ru complex (Figure 3, **14**) in combination with KOH (Table 5, entries 1-3).^[23a] The fastest catalyst reported in the TH of α,β -unsaturated carbonyl compounds was reported by Baratta and co-workers (Figure 3, **15**).^[23b] Using only 0.05 mol% of **15** in combination with K_2CO_3 as base, full conversions were achieved after less than a minute of reaction time (Table 5, entries 4-5). The TOF of this system was reported to be up to $3.3 \times 10^5 \text{ h}^{-1}$. This is the highest TOF reported to date in the transfer hydrogenation field. A lower TOF of 1828 h^{-1} was observed in the TH of substrate **8o** (Table 5, entry 17) when the amine in the catalyst was substituted with a tolyl group (Figure 3, **16**) by Gong, Song and co-workers.^[23g] Later, Baratta's research group reported the synthesis of catalyst **17** (Figure 3).^[23c] This catalyst showed excellent selectivity when compound **8e** was reduced (Table 5 entry 6). Several new generation ruthenium based complexes (Figure 3,

Table 5. Transfer hydrogenation results of α,β -unsaturated carbonyl compounds by ruthenium catalyst using different alcohols as hydrogen donors.



Entry	Cat.	Loading (mol%)	Base	Substr.	Temp. (°C)	Yield ^a (%)	Time (hours)	Ref.
1	14	1.6	KOH	8o	83	96	25 ^d	[23a]
2	14	1.6	KOH	8e	83	71	24	[23a]

3	14	1.6	KOH	8f	83	87	3	[23a]
4	15	0.05	K ₂ CO ₃	8e	83	>99 ^b	30 ^e	[23b]
5	15	0.05	K ₂ CO ₃	8p	83	>99 ^b	30 ^e	[23b]
6	17	0.05	NaOiPr	8e	83	95 ^b	25	[23c]
7	18	0.1	tBuOK	8o	83	98 ^c	75 ^e	[23d]
8	19	0.025	K ₂ CO ₃	8e	82	89 ^{b/c}	1	[23e]
9	19	0.01	K ₂ CO ₃	8t	82	91 ^{b/c}	2.75	[23e]
10	20a	0.025	K ₂ CO ₃	8e	82	90 ^{b/c}	1	[23e]
11	20a	0.01	K ₂ CO ₃	8t	82	95 ^{b/c}	1.75	[23e]
12	20b	0.01	K ₂ CO ₃	8e	82	80 ^{b/c}	4	[23e]
13	20b	0.005	K ₂ CO ₃	8t	82	95 ^{b/c}	2.75	[23e]
14	20c	0.01	K ₂ CO ₃	8e	82	77 ^{b/c}	4	[23e]
15	20d	0.01	K ₂ CO ₃	8e	82	77 ^{b/c}	4	[23e]
16	20e	0.025	K ₂ CO ₃	8e	82	84 ^{b/c}	1	[23e]
17	16	0.05	NaOH	8o	82	91 ^g	1	[23g]

^aIsolated yield. ^bDetermined by GC. ^cDetermined by NMR. ^dTime in minutes. ^eTime in seconds. ^fEtOH used as hydrogen donor and solvent. ^gDetermined by GC-Mass.

structures **19-20**) were developed in the same group in 2016.^[23e] A very impressive activity was observed when aromatic ketones were used as substrates. In addition, unsaturated aldehydes **8e** and **8t** were selectively reduced to allylic alcohols with catalyst loadings down to 0.005 mol% (Table 5, entries 9-16). However, 10% to 20% of different by-products including the corresponding saturated alcohols were observed depending on the case. A complete family of these type of systems was patented the same year.^[23f] S. Kundu and co-workers used an N,N,N'-type pincer ligand which was coordinated to RuCl₂(PPh₃)₃ giving complex **18** (Figure 3).^[25] This complex was able to reduce benzalacetone (**8o**) to the corresponding allylic alcohol with 98% NMR yield (Table 5, entry 7).

2.1.1.2.2. Using HCOOH as hydrogen donor^[23e, 24]

The ruthenium complexes that have been used for the transfer hydrogenation of unsaturated carbonyl compounds using HCOOH as hydrogen donor are shown in Figure 4. These catalysts are usually activated with different bases like NH₃, Et₃N or HCOONa. The resulting combination of HCOOH and a compatible base forms buffer solutions allowing better pH control.^[25] In this context, Baratta and co-workers used the extremely active Ru-NNC phosphine substituted complex **20b**. This catalyst was capable of reducing cinnamaldehyde and one other derivative to the corresponding allylic alcohols using catalyst loadings as low as 0.05% mol (Table 6, entries 1-2).^[23e] A different active ruthenium complex based on the water soluble PTA phosphine ligand was developed by Frost and co-workers (Figure 4, complex **21**).^[24a] This complex was shown to be selective for carbonyl reduction when cinnamaldehyde and benzalacetone were used as substrates (Table 6, entries 3-4). Unfortunately, rates and selectivity were dramatically lower when chalcone was the substrate. Different protocols like *in situ* catalyst formation were also investigated. For instance, Joo and co-workers used a combination of monosulfonated triphenylphosphine as its sodium salt and Ru²⁺ (**22**) in a biphasic system which allowed them to selectively reduce unsaturated aldehydes like cinnamaldehyde, citral and the challenging croton aldehyde with very high yields (Table 6, Entries 5-7).^[24b] This catalyst was shown to be active at 30 °C as well. Joo and his group continued studying these biphasic systems and some years later they observed how the rates were increased by using iPrOH as co-solvent.^[24h] In these reactions the catalyst resides in the

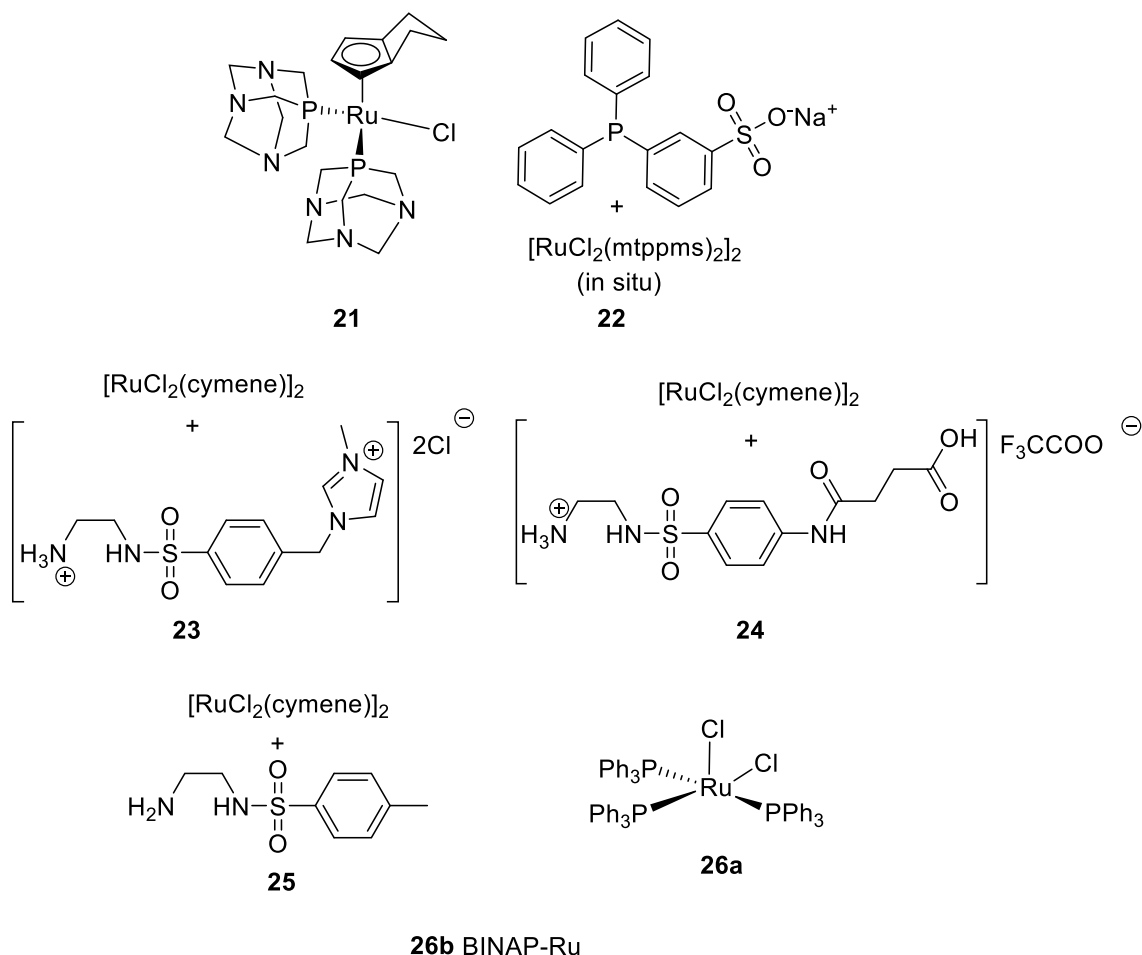
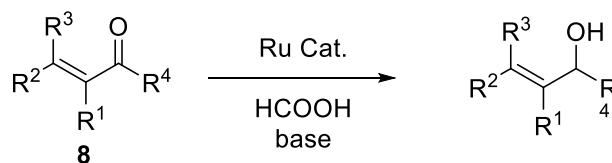


Figure 4. Non-chiral ruthenium catalysts for the transfer hydrogenation of α,β -unsaturated carbonyl compounds using HCOOH.

aqueous phase while substrate and product remain in the organic layer allowing the easy separation of the catalyst from the product once the reaction is finished. In this particular case HCOONa is in the aqueous phase, which is mixed with an organic layer of neat product or organic solvents like toluene or chlorobenzene. This protocol allowed the reduction of cinnamaldehyde to cinnamyl alcohol in 90% yield (Table 6, entry 17). The reported TOF was 160 h^{-1} . However, the selectivity was only 60% when citral (**8f**) was the substrate (Table 6, entry 18). Other *in situ* catalysts were reported by the group of Zhou.^[24d, 24e] A combination of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ with water-soluble mono-tosylated ethylenediamines was used as catalyst (Figure 4, **23-24**). With this approach using a ruthenium content of 0.5 mol%, cinnamaldehyde, citral and croton aldehyde were selectively reduced with high yields in short reaction times (Table 6, entries 10-14). A few years later DSM patented the use of tosylated diamines as ligands for the ruthenium-catalysed transfer hydrogenation of citral and ethylcitral at room temperature (Figure 4, **25**; Table 6, entry 15)^[24f]. Last but not least, Arcelli and co-workers used commercially available $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ to selectively reduce cinnamaldehyde and citral using catalyst loadings as low as 0.04 mol% and very short reaction times (Table 6, entries 8-9).^[24c] Later, the same research group compared the activity of **26a** with that of Ruthenium-BINAP.^[24g] In this work, a very uncommon hydrogen source consisting in a mixture of Et_3N and H_3PO_2 in water was used, which resulted in 65% yield in the TH of benzalacetone (**8o**).

Table 6. Transfer hydrogenation of α,β -unsaturated carbonyl compounds catalysed by ruthenium catalysts using HCOOH as hydrogen donor.



8e $R^1 = R^3 = R^4 = H$, $R^2 = Ph$

8f $R^1 = R^4 = H$, $R^2 = (CH_2)_2CH=C(CH_3)_2$, $R^3 = Me$

8o $R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = Me$

8q $R^1 = R^3 = R^4 = H$, $R^2 = Me$

8t $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = H$

Entry	Cat.	Loading (mol%)	Base	Temp. (°C)	Substrate	Yield (%)	Time (hours)	Ref.
1	20b	0.05	NH ₃	90	8e	91 ^a (88 ^b)	10	[23e]
2	20b	0.05	NH ₃	90	8t	85 ^a	48	[23e]
3	21	5	HCOONa	80	8e	100 ^{a,c}	6	[24a]
4	21	5	HCOONa	80	8o	81 ^{a,c}	24	[24a]
5	22	1.5	HCOONa	80	8e	98 ^d (92 ^b)	5	[24b]
6	22	1.5	HCOONa	80	8q	78 ^d	2.5	[24b]
7	22	1.5	HCOONa	80	8f	98 ^d (95 ^b)	7	[24b]
8	26a	0.04	Et ₃ N	rt	8f	99 ^d	30 ^f	[24c]
9	26a	0.04	Et ₃ N	rt	8e	95 ^b	30 ^f	[24c]
10	23	0.5	HCOONa	80	8e	96 ^a	30 ^f	[24d]
11	23	0.5	HCOONa	80	8f	96 ^a	3.5	[24d]
12	23	0.5	HCOONa	80	8q	96 ^a	30 ^f	[24d]
13	24	0.5	HCOONa	80	8e	80 ^a	90 ^f	[24e]
14	24	0.5	HCOONa	80	8f	31 ^a	90 ^f	[24e]
15	25	0.45	Et ₃ N	rt	8f	99 ^e	20	[24f]
16	26b	0.5	---	40	8o	65 ^{acd}	3	[24g]
17	22	1	HCOONa	rt	8e	90 ^a	1	[24h]
18	22	1	HCOONa	rt	8f	65 ^a	1	[24h]

^a Determined by GC ^b Isolated yield ^c Determined by NMR. ^d Determined by GLC. ^e Determined by HPLC. ^f Time in minutes. ^g Et₃NH⁺H₂PO₂⁻ in H₂O was the hydrogen source.

2.1.2. Iridium catalysts

Iridium is the second most used metal in homogeneous transfer hydrogenation catalysis. The high activity of the iridium-based catalysts and their high tolerance with respect to H₂O, acids and other functionalities make iridium a very appealing choice. Nevertheless, the high price of this precious metal is one of the major drawbacks.

2.1.2.1. Using iPrOH as hydrogen donor ^[26]

Back in 1978, James and Morris showed the feasibility of using Henbest's catalyst (Figure 5, complex **28**) for the selective reduction of the carbonyl moiety in cinnamaldehyde, α -methylcinnamaldehyde and croton aldehyde using iPrOH as hydrogen donor (Table 7, entries 5-7).^[26a]

Interestingly, they observed how the selectivity was dropping down when the water content in the system was increased. The authors attributed this to catalyst decomposition by moisture, which was observable by a colour change of the complex from white to yellow. Best rates and

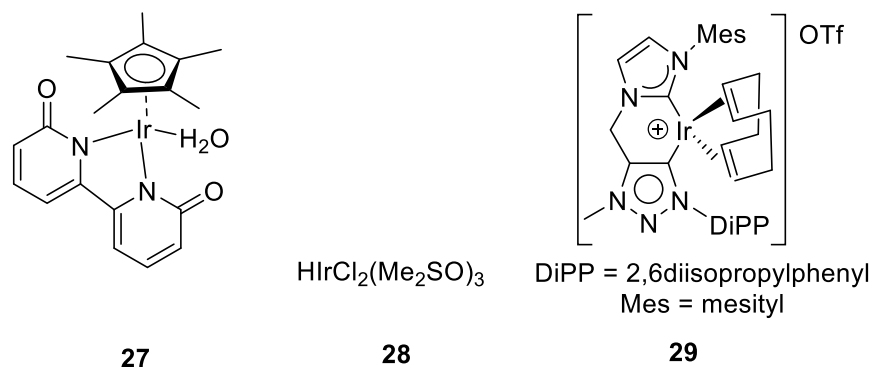
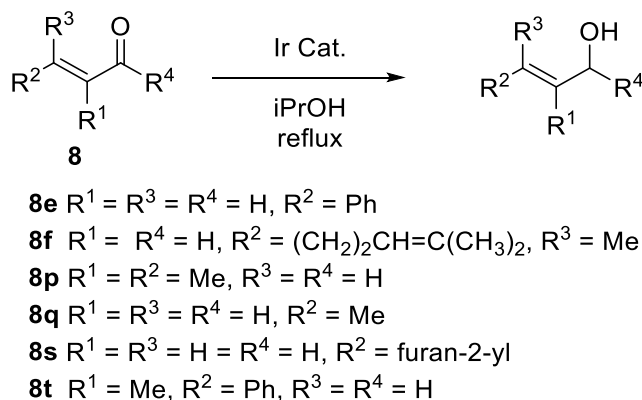


Figure 5. Iridium catalysts for transfer hydrogenation of α,β -unsaturated carbonyl compounds using iPrOH as hydrogen source.

selectivities were achieved when the isolated complex was used under dry conditions. After that, it was not until 2014 when another iridium based catalyst appeared in the literature for this type of transformation. Elsevier and co-workers synthesized a variety of Ir(COD) complexes bearing carbene ligands based on the combination of 1,2,3-triazol-5-ylidene (tzNHC) and an Arduengo-type N-heterocyclic carbene (NHC) motif.^[26b] One of these complexes (**29**) was able to catalyse the transfer hydrogenation of cinnamaldehyde with moderate selectivity (Table 7, entry 8). Very recently in 2018, the group of Li used an Iridium complex bearing a functional bipyridonate ligand (Figure 5, **27**) for the selective transfer hydrogenation under base-free conditions of the carbonyl group in a very broad variety of unsaturated aldehydes to the corresponding allylic alcohols.^[27] Some examples are summarized in Table 7 (Entries 1-4). The functional group tolerance of this reaction is remarkable, especially with regard to aromatic substrates.

Table 7. Transfer hydrogenation of α,β -unsaturated carbonyl compounds using iridium catalysts and iPrOH as hydrogen donor.



Entry	Cat.	Loading (mol%)	Temp. (°C)	Substrate	Yield (%)	Time (hours)	Ref.
1	27	0.2	120	8e	92 ^a	12	[27]
2	27	0.2	refl.	8f	94 ^a	6	[27]
3	27	0.2	refl.	8p	80 ^a	6	[27]
4	27	0.2	120	8s	92 ^a	12	[27]

5	28	4	refl.	8e	78 ^b	80 ^d	[26a]
6	28	4	refl.	8t	90 ^b	250 ^d	[26a]
7	28	4	refl.	8q	85 ^b	50 ^d	[26a]
8	29^e	1	refl.	8e	56 ^c	23	[26b]

^a Isolated yields. ^b Determined by GLC and NMR. ^c Determined by GC. ^d Time in minutes. ^e 10%mol of *t*-BuOk was used.

2.1.2.2. Using HCOOH as hydrogen donor ^[28]

The stability of certain iridium catalysts towards acids makes the use of HCOOH as hydrogen donor possible for the transfer hydrogenation of α,β -unsaturated carbonyl compounds. Therefore, more examples can be found in the last decade (Figure 6) where catalyst loadings for this type of reactions were reduced. Analogously to the previously described complexes **23**, **24**, **25** (Figure 4) in the previous section, monotosylated ethylenediamines can also be combined *in situ* with $[\text{IrCpCl}_2]_2$ as a metal source to afford an active system in the transfer hydrogenation of unsaturated carbonyl compounds. These catalysts were reported by Xiao in 2006 and by Zhou in 2011 (Figure 6, **31**, **35** respectively).^[28a, 28c] In the first case, Xiao and co-workers tested a variety of Rh, Ru, and Ir complexes bearing monotosylated ethylenediamines derivated ligands observing TOFs up to 132000 h⁻¹ for benzaldehyde transfer hydrogenation. In addition, complex **31** (Figure 6) was shown to be very robust being stable in water and air while staying active for the selective transfer hydrogenation of the carbonyl group of a large range of unsaturated aldehydes. Some examples are summarized in Table 8 (entries 3-5). In a more recent work, Zhou modified these monotosylated ethylenediamines finding that complex **35** was very active

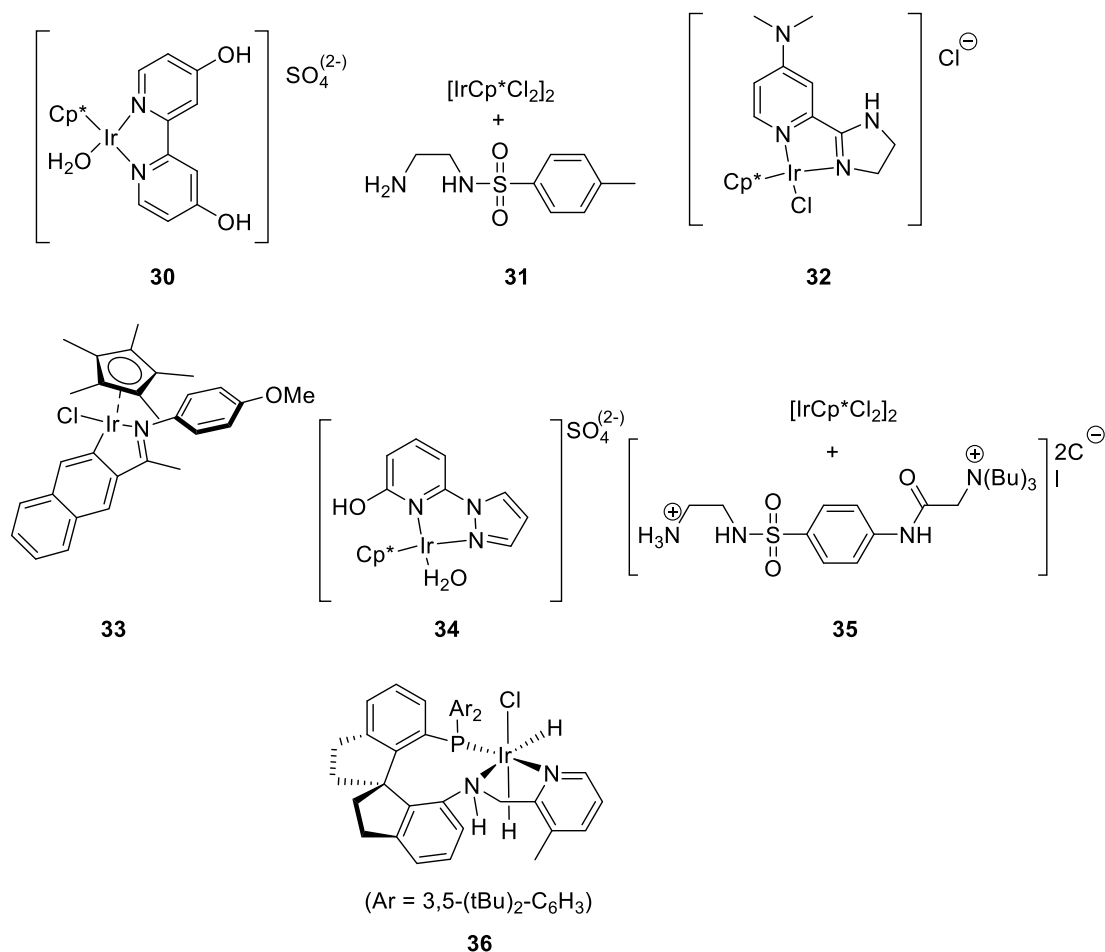
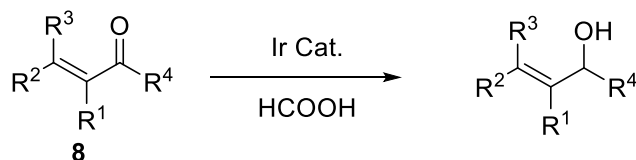


Figure 6. Iridium catalysts for the transfer hydrogenation of α,β -unsaturated carbonyl compounds using HCOOH.

and very selective when cinnamaldehyde, citral and croton aldehyde were tested as substrates.^[28c] Coordination of iridium with bipyridine and pyridine-imidazole based ligands to create active transfer hydrogenation catalysts were pursued by different groups and companies. One example of this is the work performed by the Himeda group.^[28b] The main novelty of this work was the substitution of the bipyridine ligand with hydroxyl groups. These moieties can be deprotonated at basic pH making the ligand much more electron donating, resulting in an increase of the TOF (complex **30**, Figure 6). However, selectivity towards allylic alcohols was satisfactory in only one example and pH 2,6 was needed for selectivity towards carbonyl reduction (Table 8, entry 1). An 85% yield was obtained and a TOF of 1200 h⁻¹ was observed. Later in 2015, the Dalian University of Technology patented a family of pyridine-imidazole-iridium complexes for the transfer hydrogenation of α,β -unsaturated carbonyl compounds (aldehydes and ketones).^[28c] As an example, they used complex **34** for cinnamaldehyde reduction obtaining the corresponding cinnamyl alcohol in 82% yield under mild conditions

Table 8. Transfer hydrogenation of α,β -unsaturated carbonyl compounds using iridium catalysts and HCOOH as hydrogen donor.



8e R¹ = R³ = R⁴ = H, R² = Ph

8f R¹ = R⁴ = H, R² = (CH₂)₂CH=C(CH₃)₂, R³ = Me

8o R¹ = R³ = H, R² = Ph, R⁴ = Me

8p R¹ = R⁴ = H, R² = R³ = Me

8q R¹ = R³ = R⁴ = H, R² = Me

8r R¹ = R³ = H = R⁴ = H, R² = 2,6,6-trimethylcyclohex-1-en-1-yl

8s R¹ = R³ = H = R⁴ = H, R² = furan-2-yl

8t R¹ = Me, R² = Ph, R³ = R⁴ = H

7a R¹ = Ph, R² = Me

7c R¹ = Ph, R² = CH(CH₃)₂

7q R¹ = *p*-MePh, R² = Me

Entry	Cat.	Loading (mol%)	Base	Temp. (°C)	Substrate	Yield ^a (%)	Time (hours)	Ref.
1	30	0.05	HCOONa	40	8e	85 ^b	8	[28b]
2	31	0.02	HCOONa	80	8e	97	3	[28a]
3	31	0.02	HCOONa	80	8f	97	4	[28a]
4	31	0.02	HCOONa	80	8q	>99	1	[28a]
5	31	0.02	HCOONa	80	8t	98	6 ^c	[28a]
6	32	0.02	---	80	8e	95	18 ^c	[28f]
7	32	0.02	---	80	8t	91	20 ^c	[28f]
8	33	0.1	HCOONa	80	8e	89	6	[28d]
9	33	0.1	HCOONa	80	8t	92	6	[28d]
10	33	0.1	HCOONa	80	8f	90	6	[28d]
11	33	0.1	HCOONa	80	8o	58	6	[28d]
12	33	0.1	HCOONa	80	8r	66	6	[28d]
13	34	0.25	HCOONa	50	8e	82	4,5	[28e]

14	35	0.1	HCOONa	80	8e	76 ^b	3	[28c]
15	35	0.1	HCOONa	80	8f	89 ^b	3	[28c]
16	35	0.1	HCOONa	80	8e	100 ^b	20 ^c	[28c]
17	36	1	HCOONa ^d	60	7a	99 ^a (96) ^c	8	[29]
18	36	1	HCOONa ^d	60	7c	90 ^a (94) ^c	40	[29]
19	36	1	HCOONa ^d	60	7q	98 ^a (97) ^c	10	[29]

^a Isolated yield. ^b Determined by GC/HPLC. ^c Time in minutes. ^d HCOONa (0.4 mmol) combined with EtOH (5 mL).

^e ee in brackets, determined by HPLC using a chiral column.

(Table 8, entry 13). Recently, Tang also explored this type of complex.^[28f] He found that coordinating 2-(*p*-dimethylaminopyrid-2-yl)-imidazole with iridium (Figure 6, complex **32**) resulted in a very robust complex. This complex is water and air stable and is very active for the reduction of a large variety of carbonyl compounds including cinnamaldehyde and α -methylcinnamaldehyde with excellent selectivities (Table 8, entries 6-7). TOFs up to 73800 h⁻¹ were observed when saturated compounds were used as substrates. Finally, Iridacycles were developed in the group of Xiao.^[28d] In this work, complex **33** (Figure 6) was used for the transfer hydrogenation of a large variety of substrates in H₂O buffered with the HCOOH/HCOONa couple, which also serves as hydrogen donor. Among other substrates, several α,β -unsaturated aldehyde compounds were successfully reduced. An extract of these results is shown in Table 9 (Entries 8-12). However, selectivity was poor when the target substrates were α,β -unsaturated ketones instead of α,β -unsaturated aldehydes (Table 9, entry 11). Xie and co-workers synthesized the chiral Ir-SpiroPAP complex (**36**) bearing a tridentate spiro-pyridine-aminophosphine ligand (Figure 6) which they used for the TH of propargylic ketones.^[29] This catalyst did work neither with EtOH nor with HCOOH/Et₃N but only with HCOONa in EtOH. After monitoring the reaction performed with HCOOCs in EtOH by *in situ* IR spectroscopy, they observed the conversion of HCOOCs and the simultaneous formation of EtOCO₂Cs. In addition, several alkynyl ketones were reduced with high yields and high enantioselectivities. Some examples are summarized in Table 8 (Entries 17-19).

2.1.3. Iron & other less common metals as catalysts

In addition to the abundance of Ru and Ir transfer hydrogenation catalysts in the literature, there are also publications describing the use of catalysts based on other precious metals like Rh or Ag and other transition metals like Os. Furthermore, the growing interest in greener processes as well as in cheap metals for catalysis have resulted in an exponential growth of work on catalysts based on first row transition metals. This is also true for the transfer hydrogenation of α,β -unsaturated compounds and examples of the use of complexes based on Fe, Ni and more recently Mn have appeared.

2.1.3.1. Using *i*PrOH as hydrogen donor^[21c, 23c, 30]

One of the most well-known publications in the transfer hydrogenation field stems from the work of Morris and co-workers who reported the synthesis of the chiral amine(imine)diphosphine iron complex (Figure 7, compound **37a**).^[30c] This extremely active and fast catalyst was shown to achieve TOFs up to 242 s⁻¹ at 28 °C. Unfortunately, when it was tested for the reduction of **8o** as an α,β -unsaturated ketone compound, only 55% yield of the desired product could be obtained (Table 9, entry 8). Morris and co-workers made different modifications on the catalyst, leading to the complexes **37b-d**, which were patented.^[30f-i] However, only catalysts **37c** and **37d** were capable of converting substrate **8o** in good selectivity

and yield to the desired allylic alcohol (Table 9, entries 15-16). The crystal structures of similar iron complexes bearing PNNP ligand as well as in the form of a macro cycle were reported by Mezzetti and co-workers.^[30e] By modifying the substituents of the isonitrile ligand, activity and enantioselectivity of the TH of acetophenone with complexes **38a** and **38b** were shown to be greatly enhanced. In addition to the scope of ketones, the α,β unsaturated ketone **8o** was reduced to the corresponding allylic alcohol with complete chemo-selectivity with 81% and 76% GC-Yield respectively (Table 9, entries 12-14). Other reports on iron catalysts come from Funk and co-workers who have shown that it is possible to use the Knölker complex (Figure 7, complex **40**) and a modified nitrile ligated derivative (Figure 7, complex **39**) for the transfer hydrogenation of some α,β -unsaturated aldehydes (Table 9, entries 1-4).^[30b] Although good selectivity was obtained with some starting materials, when sterically hindered L-Carvone was used as the substrate, a low yield was obtained (Table 9, entry 4). Interestingly, complex **39** was capable of the opposite reaction (Oppenauer type oxidation) when several alcohols and some α,β -unsaturated alcohols were placed in acetone as a solvent instead of iPrOH. This capability

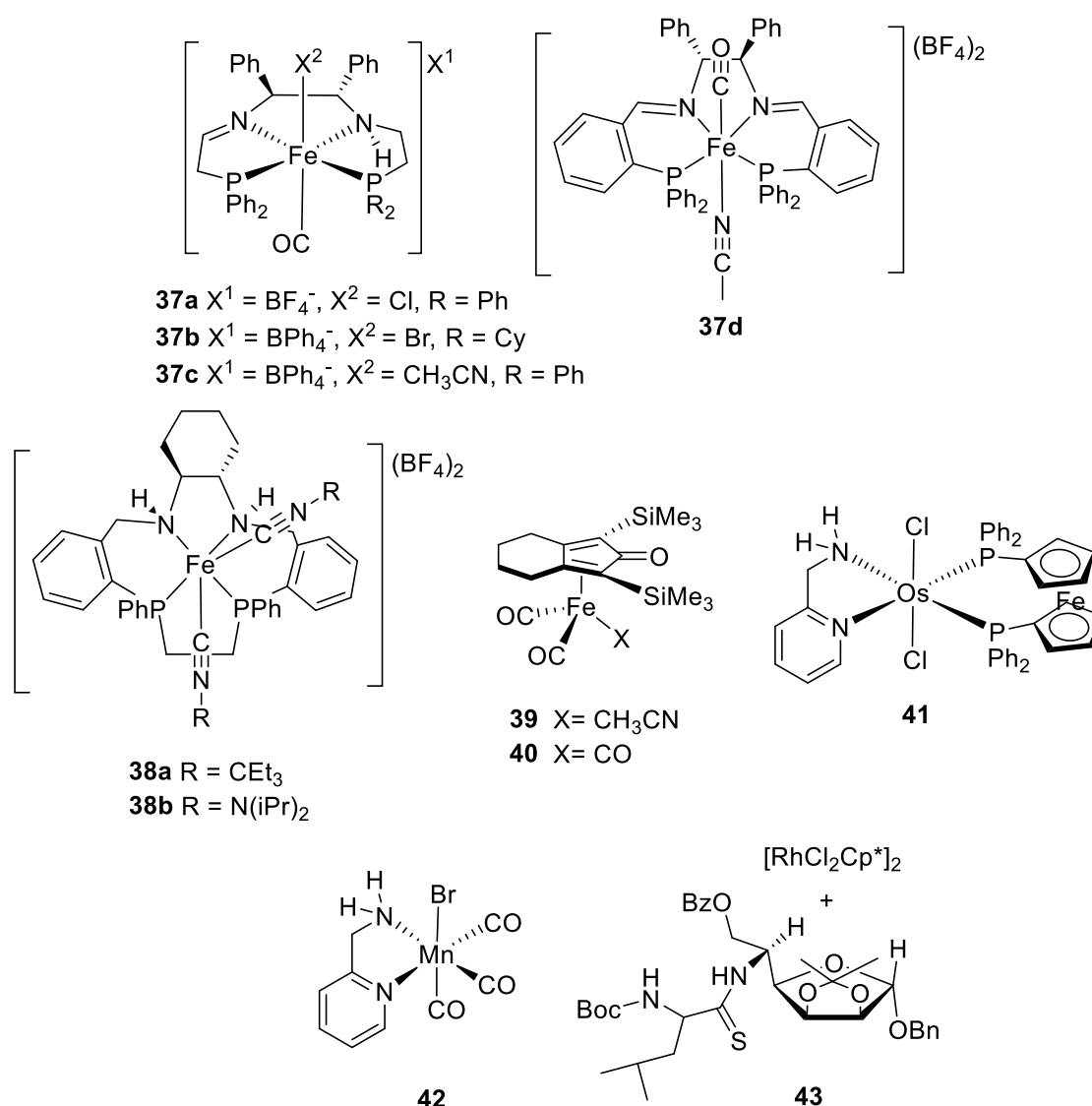
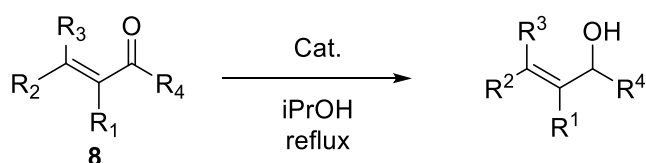


Figure 7. Transfer hydrogenation catalysts based on iron, manganese, osmium and rhodium.

is of course present in all transfer hydrogenation catalysts as they catalyse both hydrogenation as well as dehydrogenation (of isopropanol, for instance). Recently, the same research group used the Knölker catalyst **40** for the transfer hydrogenation of cinnamaldehyde (Table 9, entry 6), where 99% yield and selectivity were achieved.^[30b] However, when benzalacetone (**8o**) was the substrate only 27% of conversion with 22% selectivity was achieved (Table 9, entry 5). In this system, the use of $(\text{CH}_3)_3\text{NO}$ was required in order to generate the 16 electron active complex by CO ligand removal through oxidation of CO to CO_2 forming $(\text{CH}_3)_3\text{N}$ as side product. Analogously to the ruthenium complex **16** described in section 2.1.1, Baratta also synthesized osmium complex **41** (Figure 7).^[23c] This Os catalyst was capable of reducing cinnamaldehyde in a selective manner with catalyst loadings as low as 0.05 mol% (Table 9, entry 7). A TOF of $8.9 \times 10^4 \text{ h}^{-1}$ was observed. Sortais and co-workers synthesized phosphine-free manganese based catalyst **42** and used it successfully for the transfer hydrogenation of carbonyl groups.^[30d] Several compounds were reduced under mild conditions including 3 examples of α,β -unsaturated carbonyl compounds: benzalacetone, β -ionone and cinnamaldehyde (Table 9, entries 9-11). Very surprisingly, this catalyst was active at catalyst loadings as low as 0.5 mol% and remained active even at room temperature in some cases. The reported TOF was up to 3600 h^{-1} and the TON up to 2000. Analogously to the ruthenium complex **6b** described in the first section, Adolfsson and his team also coordinated a similar bio-based ligand to a Rh source for TH reactions (Figure 7, **43**).^[21c] Benzalacetone (**8o**) gave, via TH, the corresponding allylic alcohol in only 32% isolated yield using this catalyst at room temperature in 3 hours (Table 9, entry 17). This was mainly due to the isomerization of

Table 9. Transfer hydrogenation of α,β -unsaturated carbonyl compounds using catalysts based on iron, manganese, osmium and rhodium and alcohols as hydrogen donor.



8e $\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^2 = \text{Ph}$

8o $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{Ph}$, $\text{R}^4 = \text{Me}$

8r $\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^2 = 2,6,6\text{-trimethylcyclohex-1-en-1-yl}$

8t $\text{R}^1 = \text{R}^4 = \text{H}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Me}$

8u [Cycle] [$\text{R}_1 = (\text{CH}_2)_2\text{CH}(\text{CH}_2) = \text{R}_2$] $\text{C}(\text{CH}_2)\text{CH}_3$, $\text{R}^4 = \text{R}^3 = \text{H}$ (Perillaldehyde)

8v [Cycle] [$\text{R}_3 = \text{CH}_2\text{CHCH}_2 = \text{R}_4$] $\text{C}(\text{CH}_2)\text{CH}_3$, $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$ (Carvone)

Entry	Cat.	Loading. (mol%)	Base	Subst rate	Yield (%)	Time (hours)	Ref.
1	39	2	---	8e	98 ^a	18	[30a]
2	39	2	---	8t	97 ^a	18	[30a]
3	39	2	---	8u	85 ^a	18	[30a]
4	39	5	---	8v	35 ^a	18	[30a]
5	40	2	$(\text{CH}_3)_3\text{NO}$	8o	22 ^{bc}	24	[30b]
6	40	2	$(\text{CH}_3)_3\text{NO}$	8e	99 ^{bc}	24	[30b]
7	41	0.05	NaOiPr	8e	95 ^b	30 ^d	[23c]
8	37a	0.05	t-BuOK	8o	55 ^{be}	4 ^d	[30c]
9	42	0.5	t-BuOK	8o	90 ^{cg}	20 ^d	[30d]
10	42	0.5	t-BuOK	8r	100 ^{cg} (90 ^a) ^g	1	[30d]

11	42	0.5	t-BuOK	8e	92 ^c (80 ^a)	2	[30d]
12	38a	0.1	t-BuOK	8o	81 ^{bh}	5	[30e]
13	38b	0.1	t-BuOK	8o	76 ^{bh}	5	[30e]
14	37b	0.2	t-BuOK	8o	40 ^{bh}	20 ^d	[30g]
15	37c	0.07-0.2	t-BuOK	8o	82 ⁱ	30 ^d	[30h]
16	37d	1.8	t-BuOK	8o	70 ^j	130 ^d	[30i]
17	43	0.25	t-BuOK/LiCl	8o^k	32 ^m	3	[21c]
18	43	0.25	t-BuOK/LiCl	7a^l	90 ^m	3	[21c]

^aIsolated yields. ^bDetermined by GC. ^cDetermined by ¹H-NMR. ^dTime in minutes. ^e40% ee. ^fEtOH used as hydrogen donor and solvent. ^gIf room temperature was used, 16 hours was enough to afford 87% GC yield using substrate **8r** and 87% isolated yield using substrate **8o**. ^hTemperature was 50°C. **38a** and **38b** gave an ee of 65% and 70% respectively. ⁱTemperature was 22°C and 5% ee was obtained. ^j68% ee. ^k82% ee. ^l87% ee. ^mRoom temperature.

the formed allyl alcohol to the ketone, which was further reduced to the saturated alcohol. Propargylic ketones seemed to be much better substrates. In fact, substrate **7a** afforded propargylic alcohol in 90 % isolated yield under the same conditions (Table 9, entry 18). Similar to the ruthenium analogue, this Rh catalyst was also active for the tandem isomerization/asymmetric transfer hydrogenation of racemic allylic alcohols to the enantio enriched saturated alcohols.

2.1.3.2. Using HCOOH as hydrogen donor ^[22g, 31]

Using HCOOH as hydrogen donor is also possible with catalysts based on the 1st row transition metals. One example of this is the *in situ* approach as reported by Beller and co-workers.^[31c] They combined the ligand tetrachlorophosphine with Fe(BF₄)₄·6H₂O (Figure 8, **50**), finding this combination a very robust and efficient catalyst for the selective reduction of a wide scope of α,β-unsaturated aldehydes under base-free mild conditions and low catalyst loadings. Some representative examples are shown in Table 10 (entries 1-5). Scaling up the reactions to multi-gram scale without significant losses of the desired product was possible. The emerging trend on using tridentate-ligated complexes is also noticeable here. For example, the group of Hu reported iron based PONOP complexes (Figure 8, compounds **44a,44b**) and tested them for hydrogenation and transfer hydrogenation of different carbonyl compounds including α,β-unsaturated aldehydes (Table 10, entries 6-11).^[31e] A remarkable selectivity was found for the reduction of aldehydes over ketones in compounds that contained both functionalities. Interestingly, the use of H₂ gas as a reductant led to very similar yields if not lower for these α,β-unsaturated carbonyl compounds. Some reports on Ni catalysts can also be found in the literature. For example, Iyer and Sattar used a very simple complex, Ni[P(OPh)₃]₄ (Figure 8, complex **46**), for the selective transfer hydrogenation of different carbonyl compounds including benzalacetone and cinnamaldehyde (Table 10, entries 13-14) in acetic acid using HCOONH₄ as hydrogen source.^[31a] When iPrOH was tried as hydrogen source, the yields dropped. A few years later, the group of Sudalai synthesized a macro cyclic Nickel(II) complex (Figure 8, compound **45**).^[31b] This Ni complex was successful at 2 mol% catalyst in the reduction of cinnamylaldehyde to cinnamylalcohol with 87% yield (Table 10, entry 12). In this work, comparison with other hydrogen sources was also done. Using iPrOH as a reducing agent led to a reduced yield of cinnamyl alcohol of 53%. A number of catalysts based on late transition metals other than ruthenium and iridium can be found in the literature. For example, Li and his group screened a large variety of Ag salts, phosphine ligands, bases, additives and hydrogen sources until they

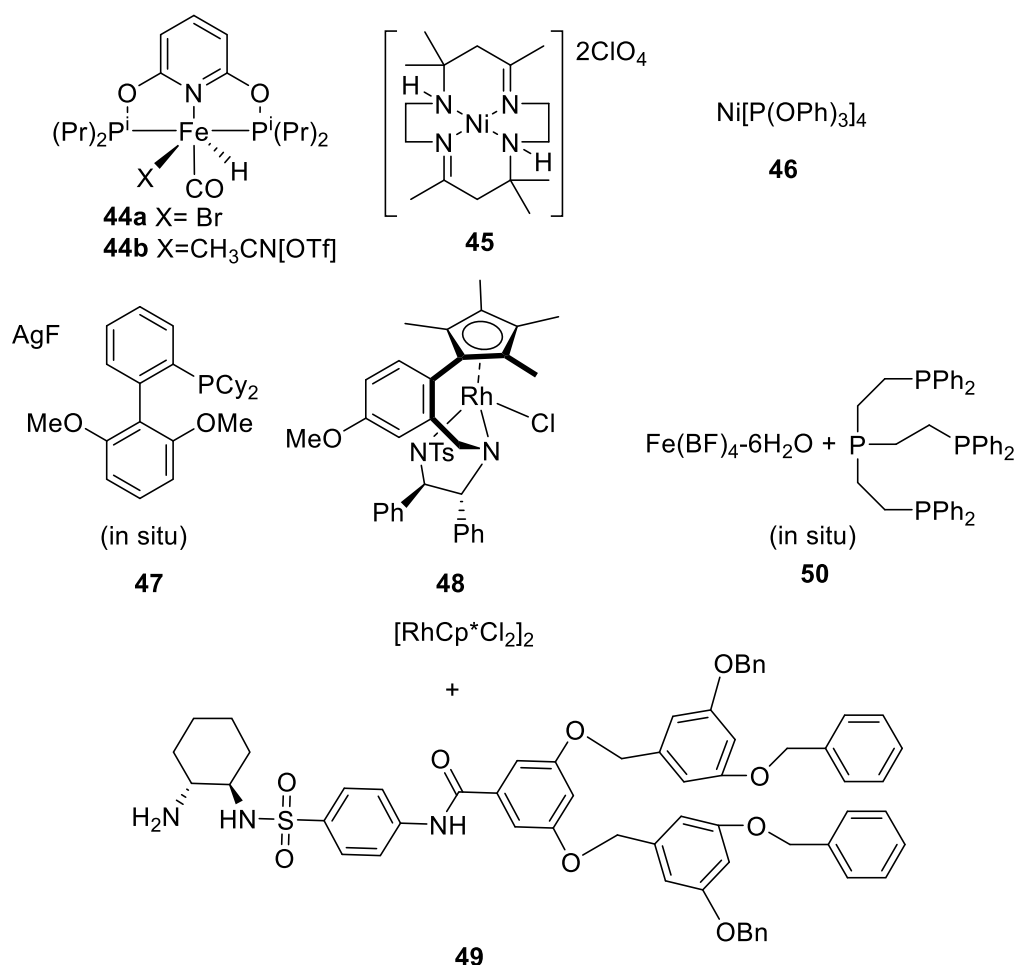
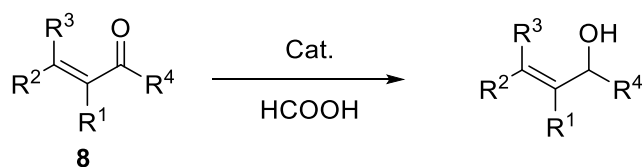


Figure 8. Catalysts based on iron, nickel, silver and rhodium for the transfer hydrogenation of α,β -unsaturated carbonyl compounds using HCOOH as hydrogen source.

found a very active combination for the transfer hydrogenation of carbonyl compounds.^[31d] The best combination was AgF as a source of metal, SPHOS as electron-rich ligand, (Figure 8, **47**) CsF as base and TfOH as an additive. The best hydrogen source was shown to be HCOOH-DIPEA. In addition to all these ingredients, PhCl was found to be useful as an extra additive for reducing the amount of DIPEA needed for high yields by formation of a microscopic organic phase. Using this approach, 82% isolated yield was obtained when cinnamaldehyde was reduced (Table 10, entry 15). The low atom efficiency in regard to the number and amount of additives is a disadvantage. Since other α,β -unsaturated aldehyde compounds like peril aldehyde or citral gave yields lower than 5%, the scope was rather limited in regard to the unsaturated carbonyl compounds. In the previously cited work of Ayad and Ratovelomanana-Vidal (Section 2.1.2) another chiral rhodium complex was tested for the transfer hydrogenation of substrate **7q** (Table 10, entry 16).^[22g] Excellent enantioselectivity was obtained in the reduction of this starting material. Finally, analogously to the dendritic system described in Section 2.1.2, Jin-Gen Deng also combined a slightly modified dendrimer with Rh (III) (Figure 8, **49**).^[31f] With this catalyst a range of pro-chiral ketones were reduced in water with HCOONa as hydrogen donor, achieving high yields and enantioselectivities. The measured TOFs were up to 384 h⁻¹. Interestingly, the catalyst could be precipitated from the reaction mixture by hexane addition and reused several times without loss in yield or selectivity.

Table 7. Transfer hydrogenation of α,β -unsaturated carbonyl compounds by catalysts based on iron, nickel, silver and rhodium using HCOOH as hydrogen donor.**8e** $R^1 = R^3 = R^4 = H, R^2 = Ph$ **8f** $R^1 = R^4 = H, R^2 = (CH_2)_2CH=C(CH_3)_2, R^3 = Me$ **8o** $R^1 = R^3 = H, R^2 = Ph, R^4 = Me$ **8q** $R^1 = R^3 = R^4 = H, R^2 = Me$ **8r** $R^1 = R^3 = R^4 = H, R^2 = 2,6,6\text{-trimethylcyclohex-1-en-1-yl}$ **8s** $R^1 = R^3 = R^4 = H, R^2 = \text{furan-2-yl}$ **8t** $R^1 = R^4 = H, R^2 = Ph, R^3 = Me$ **8u** Cycle $[R_1 = (CH_2)_2CH(CH_2) = R_2]C(CH_2)CH_3, R^4 = R^3 = H$ (Perillaldehyde)**8v** Cycle $[R_3 = CH_2CHCH_2 = R_4]C(CH_2)CH_3, R^1 = CH_3, R^2 = H$ (Carvone)**8w** $R^1 = R^3 = R^4 = H, R^2 = p\text{-(MeO)Ph}$ **8x** $R^1 = R^3 = R^4 = H, R^2 = o\text{-(O}_2\text{N)Ph}$ **7q** $R^1 = (CH_2)_4CH_3, R^2 = CH(OCH_3)COOCH_3$

Entry	Cat.	Loading. (%mol)	Base	Substrate	Yield ^a (%)	Time (hours)	Temp. (°C)	Ref.
1 ^c	50	0.4	---	8e	99 ^b	2	60	[31c]
2	50	0.4	---	8t	99 ^b	2	60	[31c]
3	50	0.4	---	8u	99 ^b	2	60	[31c]
4	50	0.4	---	8f	99 ^b	2	60	[31c]
5	50	0.4	---	8s	96	2	60	[31c]
6	44a	5	HCOONa	8e	76	6	40	[31e]
7	44a	5	HCOONa	8w	72	6	40	[31e]
8	44a	5	HCOONa	8x	65	6	40	[31e]
9	44b	5	HCOONa	8e	72	6	40	[31e]
10	44b	5	HCOONa	8w	68	6	40	[31e]
11	44b	5	HCOONa	8x	69	6	40	[31e]
12	45	2	NH ₃	8e	87	5	100	[31b]
13	46	5	NH ₃	8o	92	8	110	[31a]
14	47	5	NH ₃	8e	72	8	110	[31a]
15 ^e	47	10	DIPEA	8e	82	24	120	[31d]
16 ^f	48	0.5	Et ₃ N	7q	>99 ^d	20	30	[22g]
17 ^g	49	0.5	HCOONa	8o	94	1,3	40	[31f]

^aIsolated yields. ^bDetermined by GC ^cScaled up by a factor of 20 (10 mmol reaction) with no loss of yield or selectivity. ^dDetermined by ¹H-NMR of the crude. ^eAdditives: CsF(20 mol%), TfOH(10 mol%), PhCl (7 eq.). ^fEnantioselective affording 99% ee determined by CSP-SCF. ^gIs enantioselective, affording 52% ee determined by HPLC analysis on OD or AS column.

2.1.4. Meerwein-Ponndorf-Verley reactions ^[32]

The very first beginnings of the transfer hydrogenation field took place in the first part of the twentieth century with the studies from Meerwein and slightly later in the same year, from Ponndorf & Verley.^[32a-c] They have shown the possibility of reducing carbonyl compounds using another alcohol as a reductant via direct hydride transfer. This was possible because of the use of strong Lewis-acidic metals as catalysts i.e. Al^{3+} or Ln^{3+} . This contrasts to the weak acid character of the described metals in previous sections. In regard to the mechanism of MVP

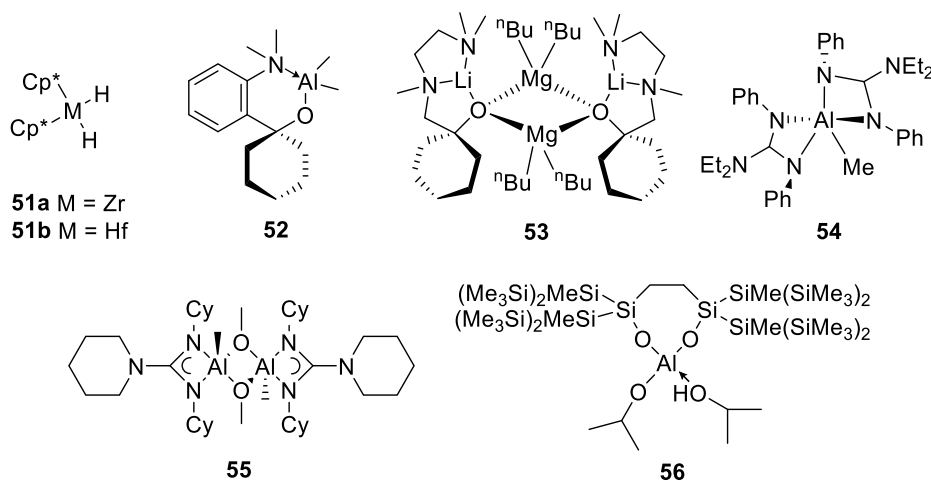
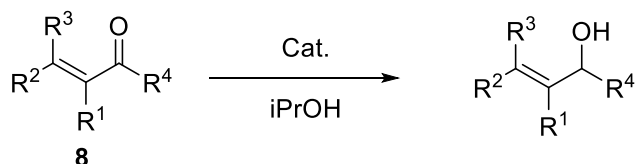


Figure 9. Aluminium, magnesium and lanthanide complexes for Meerwein-Ponndorf-Verley reduction of α,β -unsaturated carbonyl compounds.

reactions, the generally accepted catalytic cycle was shown in the introduction (Section 2.1.c Scheme 3).^[14] The main drawbacks of these MVP processes are the often required stoichiometric amounts of Lewis acid and the corresponding amounts of accumulated waste. A large amount of work has been performed in this area since then in order to increase the atom efficiency of the process.^[32i, 32k] Nevertheless, in addition to waste problems, aldol condensations, Tishchenko reactions and alcohol dehydrations are observed as side reactions. Thus, highly reactive substrate like α,β -unsaturated carbonyl compounds were not considered to be good candidates for MVP reductions. Nevertheless, a number of examples have been reported. The higher activity of all complexes cited in this section in comparison with the classical $\text{Al}(\text{O}i\text{Pr})_3$ is mainly rationalized as a consequence of preventing the strong aggregation of aluminium alkoxides. Avoiding aggregation, often by ligand fine tuning, results in more non-bridged Al alkoxides which have an accessible site for the carbonyl compound to bind to.^[32k] The first example of a MPV reduction of α,β -unsaturated carbonyl compounds comes from the work of Ishii and co-workers.^[32d] He and his group observed MVP reduction type reactions when different Zircocene and Hafnocene complexes (Figure 9, **51a**, and **51b**) were placed in contact with α,β -unsaturated carbonyl compounds in *i*PrOH. Some examples extracted from the scope are listed in Table 11 (Entries 1-7). A major contributor in recent years has been the group of Wei who reported X-ray structures of 3 different types of aluminium and magnesium based complexes (Figure 9, complexes **52** - **55**).^[32e-h] These complexes have shown moderate to good selectivities when citral and cinnamaldehyde were used as substrates affording 68% - 93% NMR yields (Table 11, entries 12-19). Krempner reported the use of another aluminium-based complex containing a bis-silanol ligand (Figure 9, complex **56**).^[32l] Diffusion experiments (^1H -

DOSY NMR spectroscopy) in C₆D₆ confirmed its monomeric structure in solution. An X-ray structure confirmed that this compound was even monomeric in the solid state. This complex was shown to be very active for a large variety of aliphatic and aromatic carbonyl compounds including some α,β -unsaturated carbonyl compounds (Table 11, entries 1-3). The reaction could be performed with as little as 0.2 mol% catalyst loading. This method showed a high tolerance for different heteroatoms and other functional groups such as nitriles, nitro group, halides or esters. Multi-gram-scale reductions of several compounds including citral were successfully achieved affording isolated yields between 86% and 97%.

Table 8. Meerwein-Ponndorf-Verley reduction of α,β -unsaturated carbonyl compounds.



8e R¹ = R³ = R⁴ = H, R² = Ph

8f R¹ = R⁴ = H, R² = (CH₂)₂CH=C(CH₃)₂, R³ = Me

8o R¹ = R³ = H, R² = Ph, R⁴ = Me

8q R¹ = R³ = R⁴ = H, R² = Me

8t R¹ = Me, R² = Ph, R³ = R⁴ = H

8y [Bicyclo] [3.1.1] [R¹ = CHC(CH₃)₂(CH₂)CHCH₂ = R²], R³ = R⁴ = H (Myrtenal)

Entry	Cat.	Loading. (% mol)	Substrate	Yield ^a (%)	Time (hours)	Temp. (°C)	Ref.
1	56	1	8e	>99	24	80	[32i]
2	56	0.5	8f	>99	24	80	[32i]
3	56	0.5	8y	90	24	80	[32i]
4	51a	2	8q	91	8	130	[32d]
5	51a	2	8e	91	8	130	[32d]
6	51a	2	8o	90	8	130	[32d]
7	51a	2	8t	72	8	130	[32d]
8	51b	2	8q	92	8	130	[32d]
9	51b	2	8e	90	8	130	[32d]
10	51b	2	8o	89	8	130	[32d]
11	51b	2	8t	68	8	130	[32d]
12	52	5	8e	79 ^b	15 ^c	refl.	[32e]
13	52	5	8f	73 ^b	15 ^c	refl.	[32e]
14	53	5	8e	68 ^b	4	refl.	[32g]
15	53	5	8f	70 ^b	4	refl.	[32g]
16	54	10	8e	90 ^b	2	110	[32f]
17	54	10	8f	93 ^b	2	110	[32f]
18	55	5	8e^a	91 ^b	8	110	[32h]
19	55	5	8f	89 ^b	8	110	[32h]

^aIsolated yields. ^bDetermined by NMR. ^cTime in minutes

2.2. Chapter 1. Selective base-free transfer hydrogenation of α,β -unsaturated carbonyl compounds using EtOH or iPrOH as Hydrogen source.

2.2.1. Introduction

Despite of all research performed on exploring the transfer hydrogenation of α,β -unsaturated aldehydes, not many catalysts have been reported to succeed when croton aldehyde is the targeted substrate. With heterogeneous catalysis selectivities higher than 90% are rare. Better results can be achieved with homogeneous systems. As was already described in the previous section, Ruthenium based catalyst are the metal of choice, always combined with hydrogen sources different to EtOH. Reports on the use of EtOH as hydrogen donor for the TH of saturated ketone or aldehyde containing compounds are scarce. To date, only 4 examples of organometallic complexes based on Ni, Ru, Rh and Ir were reported to be active with EtOH as both the reductant and the solvent (Figure 1).^[33] None of them was studied for the TH of unsaturated ketones or aldehydes. To the best of our knowledge, no homogeneous catalyst has been reported that fulfills all the desired requirements: being selective, cost-effective, robust and readily available.

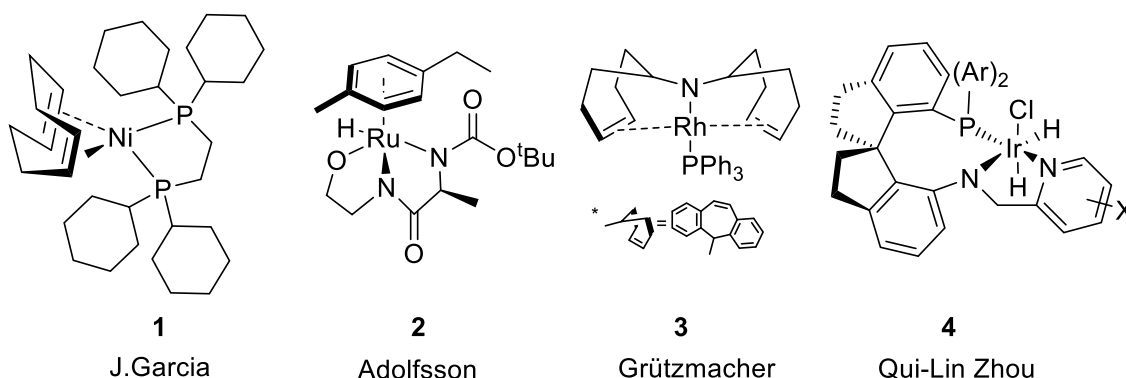


Figure 1. Active complexes reported for the transfer hydrogenation of aldehydes and ketones with ethanol as hydrogen source.

2.2.2. Objectives

- Screening and synthesizing catalysts which could be potential candidates to be active in the selective transfer hydrogenation of α,β unsaturated carbonyl compounds.
- Perform a comparison of its activity with other alcohols as hydrogen donors.
- Explore the scope and the limits of the most suitable system found.

2.2.3. Results and discussion

2.2.3.1. Catalyst screening

The screening began with the catalysts represented in Figure 2 and crotonaldehyde as substrate. Due to its reported activity with EtOH, Rh amide **3** was selected. Then, because of the experience in the group with ruthenacycles, complex **5**^[34] was also tested. The Shvo catalyst (**6a**)^[35] and its iron derivative the Knöller complex (**6b**)^[36] are also interesting candidates because of their reported activity in the TH of other compounds. Ru-MACHOTM-BH (**7**)^[37] is a well-known catalyst that has been reported to hydrogenate hardly reducible functionalities like esters or nitriles,^[38] it has been used to catalyse the hydrogen production from primary and secondary alcohols,^[39] and for other types of reactions.^[40]

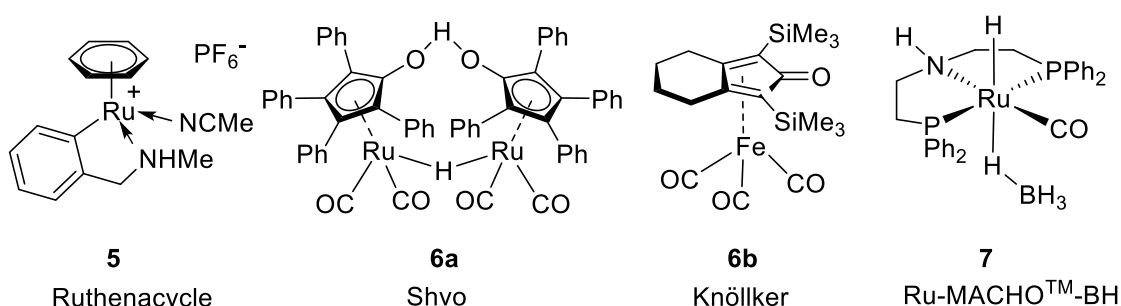


Figure 2. Selected complexes for the catalyst screening.

Rh amide **3** was shown to be extremely active and selective for the TH of croton aldehyde using EtOH as hydrogen donor (Table 1, ntry 1). However, the high activity that the catalyst is endowed with, is at the expense of the fast decomposition of the catalyst. This fact, combined with the high price of the Rh metal and the ligand makes this system not to fit our requirements. The use of ruthenacycle **5** after activation with tBuOK gave full conversion of starting material but with no selectivity towards the allylic alcohol (Table 1, entry 2). These results are likely caused by the susceptibility of α,β -unsaturated carbonyl compounds towards basic media. In fact, a variety of products was formed when crotonaldehyde was treated with tBuOK at reflux in EtOH. Since most transfer hydrogenation catalysts that operate on the Noyori mechanism need a base to initiate the reaction and also to increase the rate,^[12] not many catalysts are available.^[41] One catalyst that is reported to be active without base is the Shvo catalyst **6a**.

Table 1. Catalyst screening for transfer hydrogenation of croton aldehyde. ^a

Entry	Cat.	Additive	Temp. [°C]	Conv. ^b [%]	Yield ^b [°C]	
1 ^c	3	-	rt	>99	>99	
2	5	tBuOK	rt	>99	0	

3	6a	-	45	40	32
4	6b	(CH ₃) ₃ NO	50	66	8
5	7	-	refl.	>99	70
6 ^d	7	-	refl.	>99	97

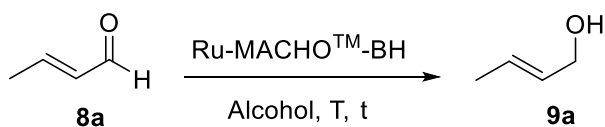
^aReaction conditions: substrate(1mmol), solvent EtOH (10 ml), reaction advance monitored by TLC and GC, system equipped with an exist for gases, overnight reactions. ^bDetermined by GC with dodecane as internal standard.^c Reaction time: 2 minutes. ^d*i*-PrOH used as hydrogen source and solvent

However, when this catalyst was tried for the TH of crotonaldehyde with EtOH as H₂ source, it was not possible to optimize the conditions to increase the low yield observed (Table 1, entry 3). Using its iron analogue, the Knölker catalyst **6b**, did not improve matters. Likely, after the conversion of the additive needed for catalyst activation, (CH₃)₃NO into (CH₃)₃N, non-desired reactions are catalysed by the basic character of (CH₃)₃N. Gratifyingly, the treatment of crotonaldehyde with Ru-MACHOTM-BH (**7**) in EtOH led to 70% yield of allylic alcohol in only 10 minutes. Considering all possible by-products as result of different condensations between croton aldehyde, crotyl alcohol, EtOH and acetaldehyde it is surprising this obtained selectivity.

2.2.3.2. Optimization of the Reaction Conditions

After having established that Ru-MACHOTM-BH performs the required reaction in good selectivity, the conditions were optimized in order to enhance conversion and selectivity (Table 2). Reducing the temperature to room temperature showed very low conversion in an overnight experiment. (Table 2, entry 1). Increasing the temperature led to much higher conversion and the time could be reduced to 10 minutes (Table 2, entries 2 and 3). Next, it was possible to reduce catalyst loading to 0,1 mol% with no significant loss in yield (Table 2 entry 4). With lower catalyst loading no conversion was observed. In the light of these results, standard

Table 2. Optimization of reaction conditions for the Ru-MACHOTM-BH catalysed transfer hydrogenation of croton aldehyde to crotyl alcohol.^a



Entry	Alcohol	Temp. [°C]	Cat. [mol%]	Time [min]	Conv. ^b [%]	Yield ^b [%]
1	EtOH	rt	1	16h	12	5
2	EtOH	50	1	60	98	56
3	EtOH	refl.	1	10	>99	70
4	EtOH	refl.	0.1	10	>99	69
5	EtOH/H ₂ O ^c	refl.	1	60	39	14

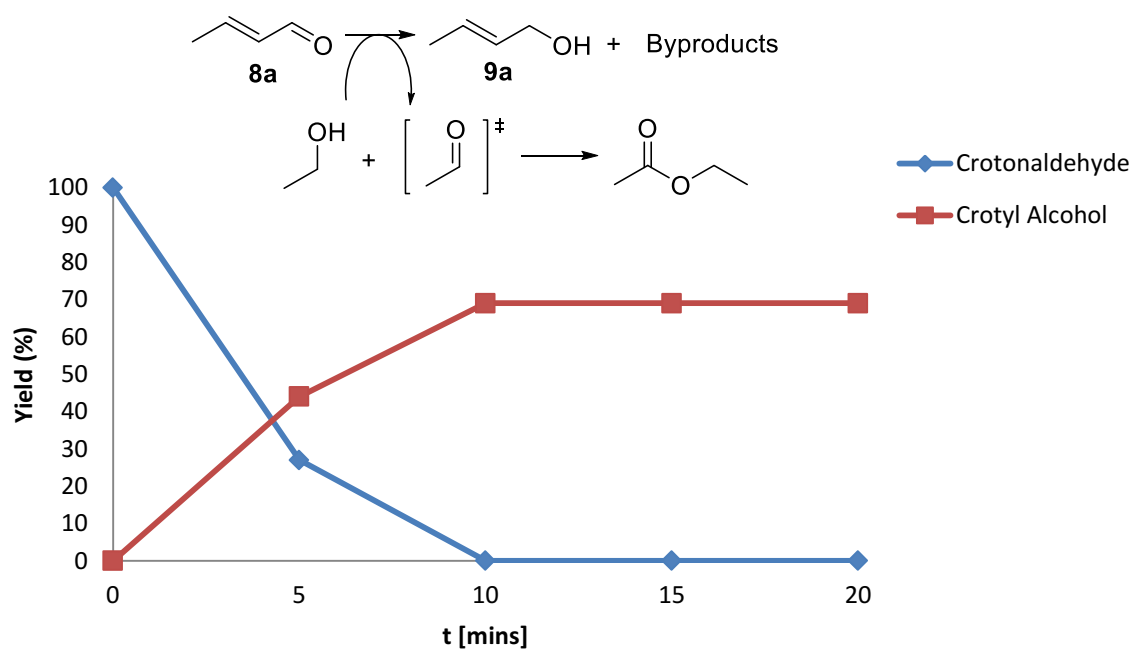
6	iPrOH	refl.	1	6.5	>99	>99
7 ^d	iPrOH	refl.	0.1	6.5	>99	>99 (89) ^e
8	Cyclohexanol	90	0.1	6.5	>99	>99

^aReaction conditions: 4.7 mmol croton aldehyde, 20 mL alcohol. ^bDetermined by GC with dodecane as internal standard. ^cRatio: EtOH/H₂O=9/1. ^d 24.3 mmol croton aldehyde (2 mL), 80 mL solvent. ^eIsolated yield.

conditions were defined as the ones in Table 2 entry 4. The sensitivity of the catalyst to water was studied when a mixture of EtOH/H₂O (9/1) as H₂ source was used instead. In this case, the rate decreased tremendously. In fact, 3 hours were needed to convert 47% of the substrate and only afforded 17% yield of the desired product (Table 2, entry 5). Other secondary H₂ sources were also studied. For example, when iPrOH was used higher conversion and selectivity were obtained (Table 2, entries 6-7). The robustness of the system was proven when the reaction was scaled up to multi-gram scale with no loss of conversion or selectivity (Table 2, entry 7). In order to isolate crotyl alcohol from the media an azeotropic distillation was needed. After filtering the catalyst with a pad of silica enough pentane was added to the crude to create the azeotrope EtOH-Pentane, then removing the solvents was possible at temperatures lower than 50°C. This protocol allowed isolating 89 % of crotyl alcohol. A heavier secondary alcohol like cyclohexanol was also used in a successful manner (Table 2, entry 8). In this case cyclohexanone was detected as by-product from the TH process. Cyclohexanol is a good candidate for easier isolations when the products have low boiling points.

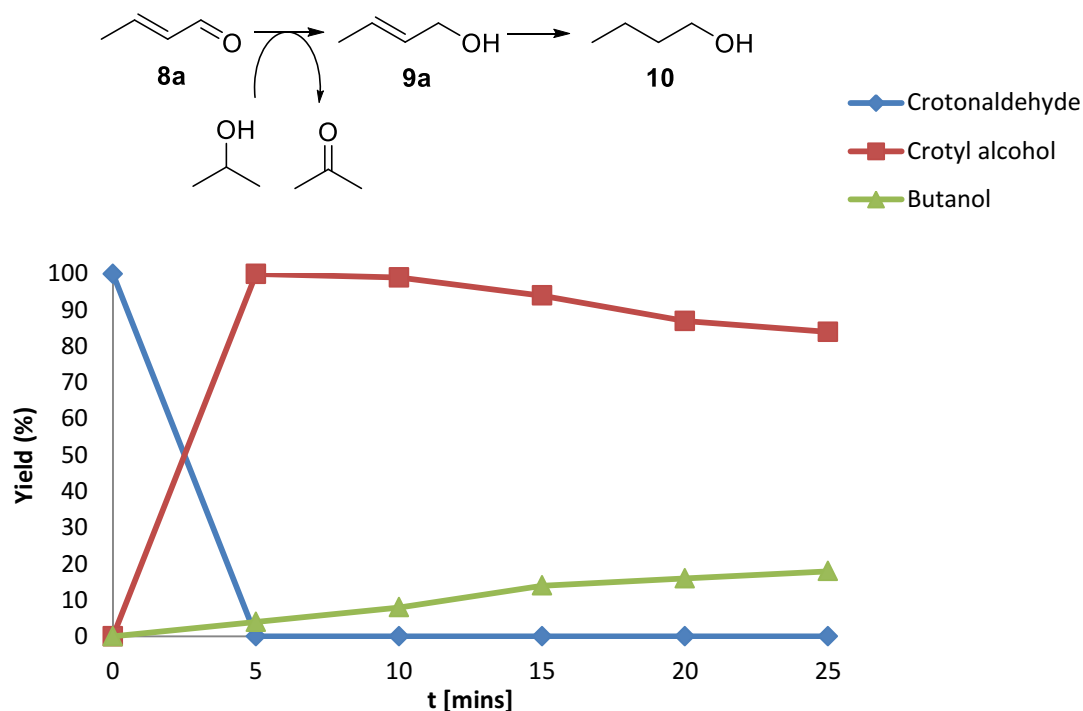
2.2.3.3. Hydrogen source comparison

Next, the reactions with EtOH and iPrOH as hydrogen sources were monitored for comparison (Schemes 1 and 2). Differences in rates, yields and selectivity were observed. By using EtOH as H₂ source a large amount of ethyl acetate was formed as the main by-product. This occurs



Scheme 1. Monitoring reaction of the transfer hydrogenation in EtOH

because the acetaldehyde that is formed can react immediately with another molecule of EtOH leading to one hemiacetal molecule which gets further dehydrogenated to ethyl acetate. In



Scheme 2. Monitoring reaction of the transfer hydrogenation in *i*-PrOH

previous publications where EtOH is used as a reductant ethyl acetate formation is also described.^[33c, 42] When highly reactive croton aldehyde and crotyl alcohol are in the media, they can react with acetaldehyde as well, leading to some unidentified by-products detected in this reaction. In addition, the acetaldehyde formation in this type of hydrogen transfer reactions is also reported by Krische et.al. He and his group used this formed acetaldehyde in the EtOH dehydrogenation as electrophile in the presence of dienes as nucleophiles for other type of condensations.^[43] On the other side, acetone was the only product from the dehydrogenation of *i*PrOH. Furthermore, the main by-product formed in this reaction was butanol. The mechanism of formation of butanol is unclear. It could either be a direct reduction of the double bond, or alternatively, an isomerization of crotyl alcohol to butyraldehyde occurs first, followed by its hydrogenation to butanol. The possibility of reducing the double bond is likely because of the slightly higher reflux temperature of *i*PrOH. Nevertheless, the rate in this secondary reaction is slow enough that when the reaction is stopped when full conversion of crotyl aldehyde, selectivity obtained to crotyl alcohol is near 100% (Scheme 2).

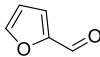
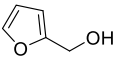
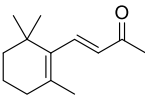
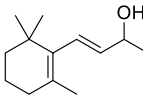
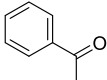
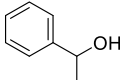
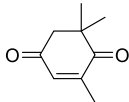
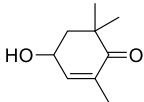


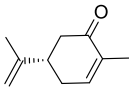
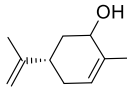
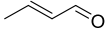
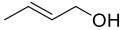
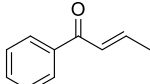
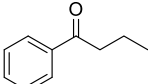
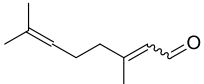
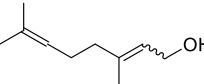
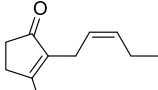
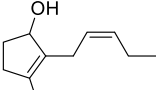
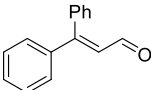
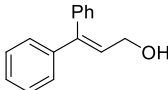
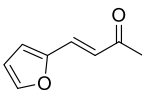
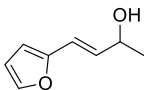
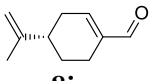
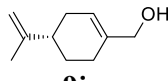
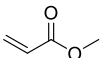
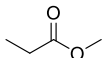
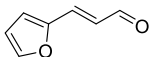
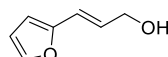
2.2.3.4. Scope and limitations

Next, having in hand a new protocol for the selective transfer hydrogenation of croton aldehyde with both EtOH and *i*PrOH we decided to continue with the exploration of the scope and the limitations of this system using defined standard conditions (Table 3). Excellent conversions and yields were achieved when targeted substrates were aliphatic and aromatic aldehyde and

ketone containing compounds (Table 3, entries 1-6). 1-octanal (**8b**) and 3-octanone (**8c**) as model compounds for aliphatic substrates were reduced to the corresponding aliphatic alcohols using EtOH as H₂ source resulting in 89% and 80% of isolated products respectively (Table 3 entries 1-2). An aromatic model compound like benzaldehyde (**8d**) was smoothly reduced to corresponding alcohol in both EtOH and iPrOH as hydrogen sources with 71% and 87% isolated yields respectively (Table 3, entry 3). Quantitative yield was obtained when acetophenone (**8f**) as substrate and iPrOH as hydrogen source were used (Table 3, entry 4). When α,β -unsaturated carbonyl compounds are used as substrates, the desired allylic alcohols are harder to obtain since is necessary to avoid aldol condensations and over reduction reactions. Gratifyingly, the protocol developed herein allowed moderate to high yields and selectivities towards allylic alcohols (62% to 99% isolated yields) in the TH of unsaturated carbonyl compounds (Table 3, entries 7-14). For example, citral (**8h**) was smoothly converted in to a mixture of geraniol and nerol with 97% isolated yield with both hydrogen sources. Next, several α,β -unsaturated ketones were also converted into allylic secondary alcohols (Table 3, entries 15-18). Again, using β -Ionone as an unsaturated ketone-model compound, EtOH turned out to be an excellent hydrogen donor affording β -Ionol with 91% yield (Table 3, entry 15). Worth of highlighting is that when ketoisophorone (**8p**), a substrate containing 2 differently conjugated carbonyl moieties, was used, only the less sterically demanding one was reduced affording the corresponding alcohol with 84% isolated yield (Table 3, entry 16). Accordingly, a multiplet at 4.5 ppm in the ¹H-NMR was observed corroborating this. (See experimental section). By contrast, using a family of different Noyori ethylenediamine derivatized systems in basic media, more sterically hindered carbonyl was reported to be reduced in a transfer hydrogenation process.^[21e] Noticeable, non- conjugated C=C double bonds remained unreduced in all cases (Table 3, entries 8, 10, 15, 17, 19). On the other hand cis-Jasmone was not suitable for the TH protocol. In fact, this compound remained unconverted even after increasing the catalyst loading to 1 mol%. The same result was obtained when simplified substrate 2,3-dimethylcyclopent-2-en-1-one was tried for the TH. Reducing the carbonyl moiety in this substrate is not favoured thermodynamically because this transformation has a positive Gibbs free energy (*vide infra*). Interestingly, when (E)-1-phenylbut-2-en-1-one (**8r**) was submitted to our protocol selectivity towards the reduction of the C=C double bond was favoured in comparison to the C=O bond. Indeed, 74% GC yield of the saturated ketone with less than 10%

Table 3. Substrate scope of the Ru-MACHOTM-BH catalysed transfer hydrogenation.^a

$ \begin{array}{c} \text{R}_2 \\ \diagup \quad \diagdown \\ \text{R}_1 \text{C} = \text{C} \text{C} = \text{O} \text{R}_4 \\ \diagdown \quad \diagup \\ \text{R}_3 \end{array} \xrightarrow[\text{Alcohol, reflux}]{\text{Ru-MACHO}^{\text{TM}}\text{-BH}} \begin{array}{c} \text{R}_2 \\ \diagup \quad \diagdown \\ \text{R}_1 \text{C} = \text{C} \text{C}(\text{OH}) \text{R}_4 \\ \diagdown \quad \diagup \\ \text{R}_3 \end{array} $							
Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1			89 ^b	12			95 ^e
	8b	9b			8l	9l	
2			80 ^b	13			94 ^e
	8c	9c			8m	9m	
3			87 ^b 71 ^b	14			62
	8d	9d			8n	9n	

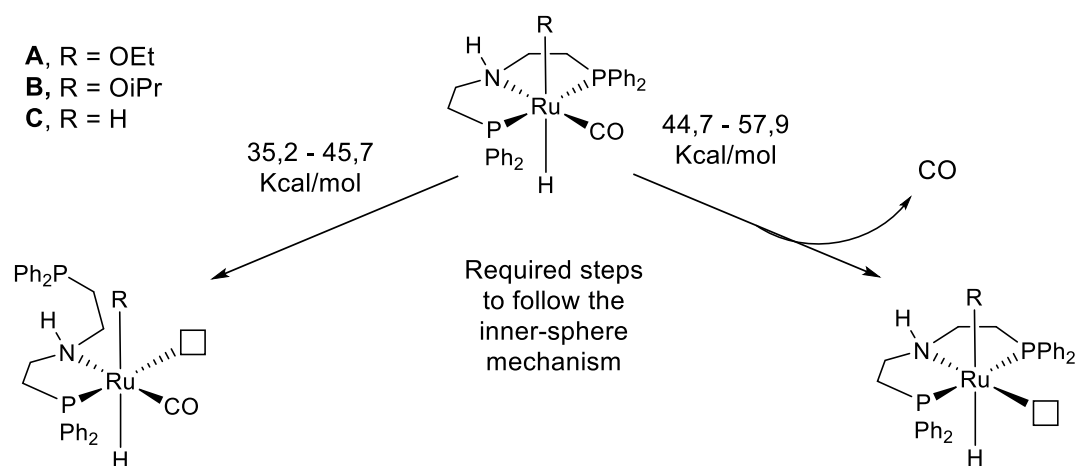
4			79	15			91 ^{b,e}
	8e	9e			8o	9o	
5			>99	16			84 ^e
	8f	9f			8p	9p	
6			72 ^e	17			64 ^e
	8g	9g			8q	9q	
7			89 ^c	18			74 ^{d,e}
	8a	9a			8r	9r	
8			97 ^{b,e}	19			0 ^b
	8h	9h			8s	9s	
9			97	20			>99 ^d
	8i	9i			8t	9t	
10			73 ^e	21			66 ^{d,b} 35 ^d
	8j	9j			8u	9u	
11			>99				
	8k	9k					

^a Reaction Conditions: substrate (4.7 mmol), *i*-PrOH (20 mL), cat. loading 0.1% mol, reflux, reaction run until starting material was consumed (from 2 to 30 minutes depending on the substrate), monitored by TLC and CG using dodecane as internal standard. All yields are isolated unless mentioned otherwise. ^b Isolated yield of reaction in EtOH (20 mL). ^c Crotonaldehyde (24.1), *i*PrOH (80 mL), reflux, 6.5 minutes. ^d CG-yield. ^e Catalyst loading 0.5 mol%.

of desired allylic alcohol was formed (Table 3, entry 16). Probably this is a consequence of the steric hindrance caused by the phenyl ring. This effect was also noticed in other cases like 4-keto-isophorone (**8p**) or (E)-1-phenylbut-2-en-1-one (**8r**). Also this effect explains the moderate yield (64% isolated yield) when L-Carvone (**8q**) was used as substrate (Table 3, entry 17). In addition to the scope, methyl acrylate (**8u**) as representative example for an α,β -unsaturated ester was submitted to our protocol with both hydrogen sources to find that only the C=C double bond moiety was reduced (Table 3, entry 21).

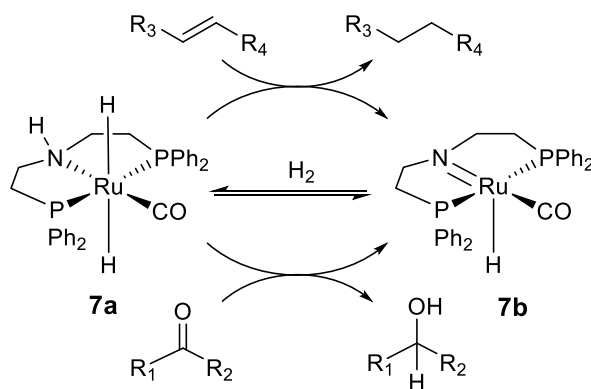
2.2.3.5. Mechanism and computational calculations

In the light of the experimental results obtained, Prof. Haijun Jiao and his group performed DFT calculations on the TH of the most interesting substrates as part of a collaboration with us.^[44] Here, the most important conclusions are briefly summarized. Interested readers can check reference number [44] for more details. These DFT studies were performed on Ru-MACHOTM-BH (**7a**) and its dehydrogenated counterpart (**7b**) as the real active complex by using the Gaussian 09 program.^[45] All structures were optimized at the B3PW91^[46] level with the TZVP^[47] basis set (LANL2DZ^[48] for metals). No transition states with one or any imaginary frequencies or modes were used for characterizing all the optimized structures as either minimums. Also the transition states always connect the initial and the final states. The thermal correction to Gibbs free energy at 298 °K from the frequency analysis was added to the total electronic energy. Based on earlier works on hydrogenation using Fe and Ru based catalysts bearing a PNP ligand^[49] an outer-sphere mechanism is proposed. (See section 2.1, scheme 2). Nevertheless, it is worth to remark that 2 examples of prevalence of an inner-sphere mechanism with comparable catalysts have been published.^[50] In one of these the ruthenium hydrogenation catalyst bears a NH moiety on the ligand and the other one concerns a catalyst based on ruthenium bearing a secondary amine instead. First of all, a comparison between 2 possible mechanisms was done. For both mechanisms it is assumed that Ru-MACHOTM-BH complex releases the BH₃ moiety to form the amido-complex **7a** which is the real active agent (Scheme 3).^[38c] The reason for not needing any type of base for catalyst activation relies on the reactivity of BH₃ to form alkoxy substituted borates following the reaction $[B_2H_6 + ROH \rightarrow H_2 + B(OR)_3 + BH(OR)_2]$ thereby permanently activating the pre-catalyst **7a**.



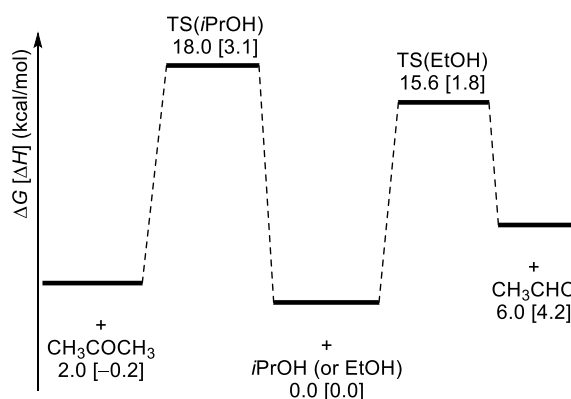
Scheme 3. Pathways to create a coordination vacant on the ruthenium complex to allow the inner sphere mechanism

In the inner-sphere mechanism the Ru-amido complex **7b** reacts with the alcohol to form the ruthenium alkoxide complex having the N atom of the ligand protonated. After that, to form a Ruthenium dihydride species a β -Hydride elimination step is a required. In this context, this reaction is only possible if a vacant site is created on the metal (Scheme 3). Only 2 options exist to create this vacant site: CO dissociation or phosphine decooordination. Whereas CO dissociation in the ethoxide, iPropoxide and amino complexes for both triplet and singlet states



Scheme 4. Proposed hydrogenation mechanism.

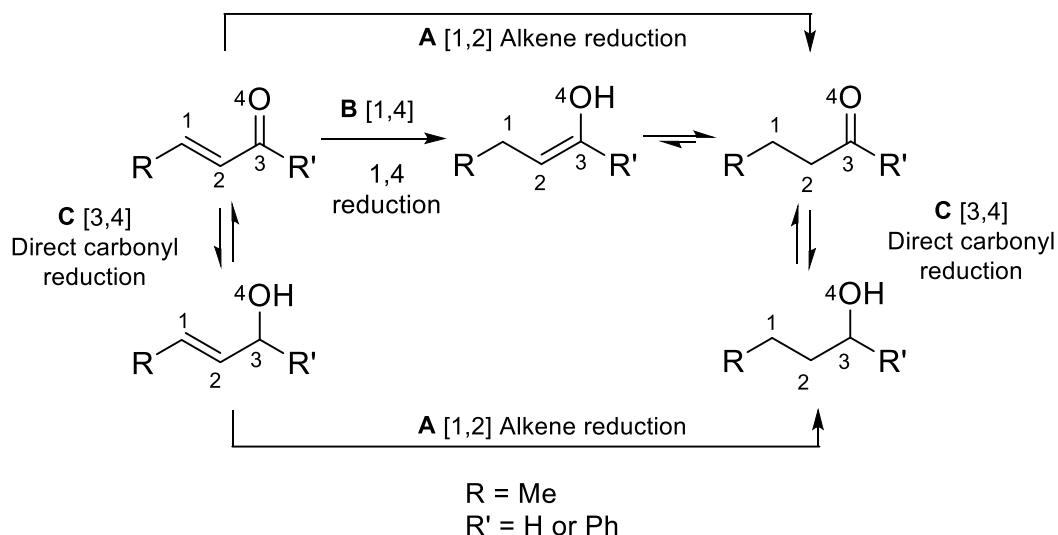
is endergonic by a range of values from 44.7 to 57.9 kcal/mol, the phosphine decoordination in the ethoxide, iProxide and amino complexes for both triplet and singlet states is endergonic by a range of values from 35.2 to 45.7 kcal/mol. Thus, the highest energy barriers which are need to be overcome are much higher in the inner sphere mechanism than the one in the outer-sphere mechanism (*vide infra*) suggesting that this pathway has a low probability. Considering now the outer-sphere mechanism and taking in account the previously done computational work^[38c] A free energy barrier of 21.3 kcal/mol for the H₂ elimination in the ruthenium amido species formation was calculated and is also slightly endergonic by 0.46 kcal/mol. The reverse reaction in which the dihydride ruthenium complex is formed has a barrier of 20.9 kcal/mol. This results show the equilibrium existing between the ruthenium species which can be easily shifted using H₂ pressure as a tool and on the other side, explains why Ru-MACHO based complexes are reported to be good hydrogenation-dehydrogenation catalysts (Scheme 4). Next, the dehydrogenation of both H₂ sources was computed (Scheme 5). Both iPrOH and EtOH dehydrogenations are endergonic by 2.0 Kcal/mol and 6.0 Kcal/mol respectively and they have an energy barrier of 15.6 Kcal/mol and 18.0 Kcal/mol respectively. From the reduced species



Scheme 5. Potential energy surface of EtOH and *i*-PrOH dehydrogenation using 7b as catalyst.

7b, the mechanistic pathway can continue via 3 different pathways, each of which leads to different products (Scheme 6). It can be seen from the scheme 6 that pathway C [3,4] results in allylic alcohol via C=O reduction, the pathway A [1,2] leads to the saturated products via C=C double bond hydrogenation and the last pathway possible is the B [1,4] which results in the enol

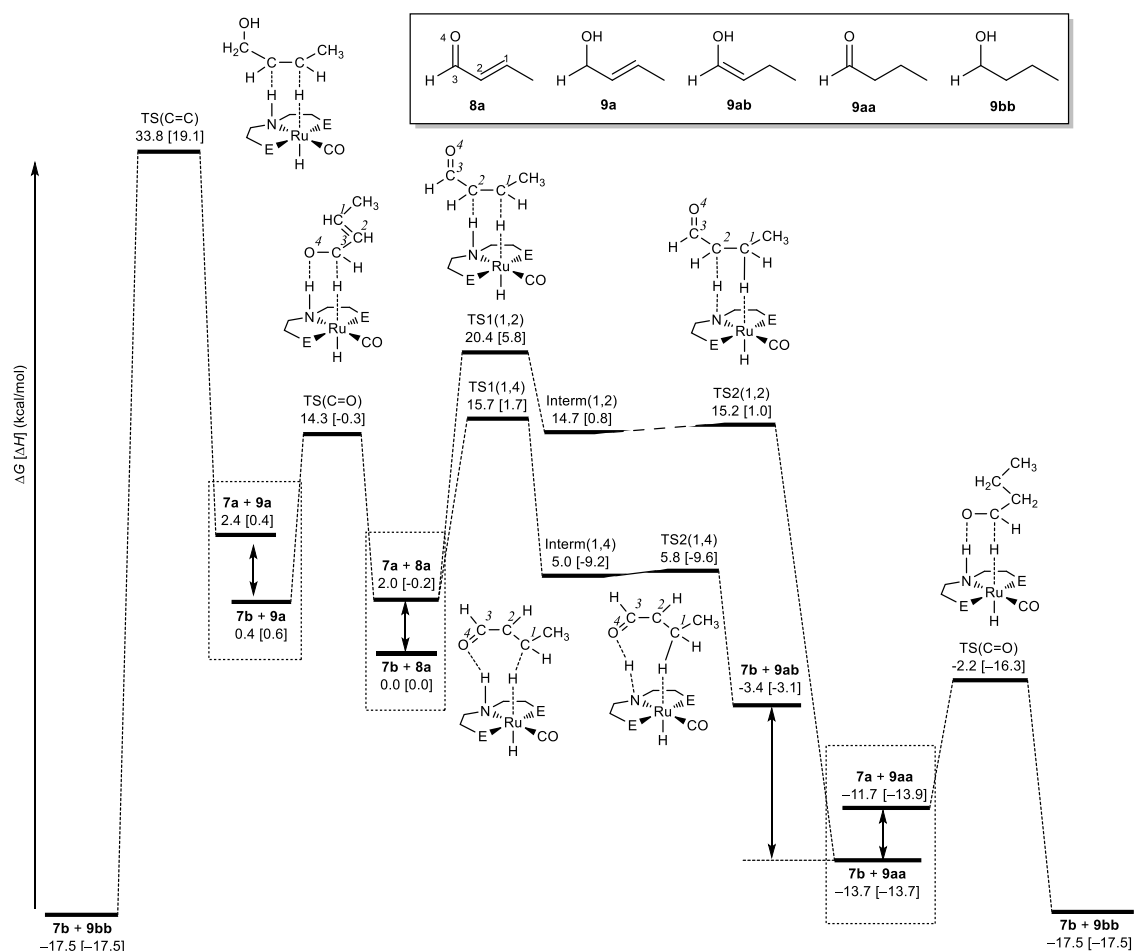
formation which can further tautomerize to the saturated carbonyl compound. Thus, is clear that starting from the α,β -unsaturated carbonyl compounds pathways A and B will lead to the same product, the saturated carbonyl compound. For facilitating the calculations and because of the more extensive use of iPrOH as hydrogen source, iPrOH was used for the calculations. The corresponding potential energy surface involved for the TH crotonaldehyde through all three



Scheme 6. Proposed hydrogenation routes

pathways was calculated and is depicted in scheme 7. Pathway C leads to crotyl alcohol **9a**. This transformation involves a hydride transfer via a concerted two-bond asynchronous transition state which has a barrier of 12.3 kcal/mol and is exergonic by 1.6 kcal/mol. On the other hand, the pathways A and B involve a stepwise mechanism. The pathway A leads to butyraldehyde, at first a hydride is transferred from Ru-H to C1 followed by the transfer of the H coming from the NH moiety to the C2. The first step has an energy barrier of 18.4 Kcal/mol with an endergonic transition state by 12.7 Kcal/mol the following proton transfer has an energy barrier of 13.2 Kcal/mol and leads to butyraldehyde via an exergonic transformation by 15.7 Kcal/mol. Finally, in the pathway B which results in (*E*)-but-1-en-1-ol (**9ab**) also the first step involves the hydride transfer from the Ru to the C1, however in this case the enolate is formed as intermediate allowing the protonation of the oxygen atom by the NH. Enolate formation has a free energy barrier of 13.7 Kcal/mol with an endergonic intermediate by 3.0 Kcal/mol. The second step has a free energy barrier of 3.8 Kcal/mol leading to the enol compound via an endergonic step by 5.4 Kcal/mol. Therefore the B pathway is kinetically more favoured than the A pathway by 4.7 Kcal/mol and the following tautomerization is exergonic by 10.3 Kcal/mol. Next, a comparison between the energy surfaces of the following hydrogenations of crotyl alcohol and butyraldehyde to butanol was done. In the case of crotyl alcohol the C=C double bond hydrogenation has a very high energy barrier of 31.4 Kcal/mol but the transformation is exergonic by 19.9 Kcal/mol. Therefore, despite of being highly favoured thermodynamically, the hydrogenation of the C=C double bond is highly kinetically hindered. On the other side, the hydrogenation of butyraldehyde via the pathway C is highly favoured with an energy barrier of 9.5 Kcal/mol and the transformation is exergonic by 5.8 Kcal/mol. Thus, butanol formation from butyraldehyde is both kinetically and thermodynamically favoured. This explains why butyraldehyde was not detected experimentally in the reaction. In

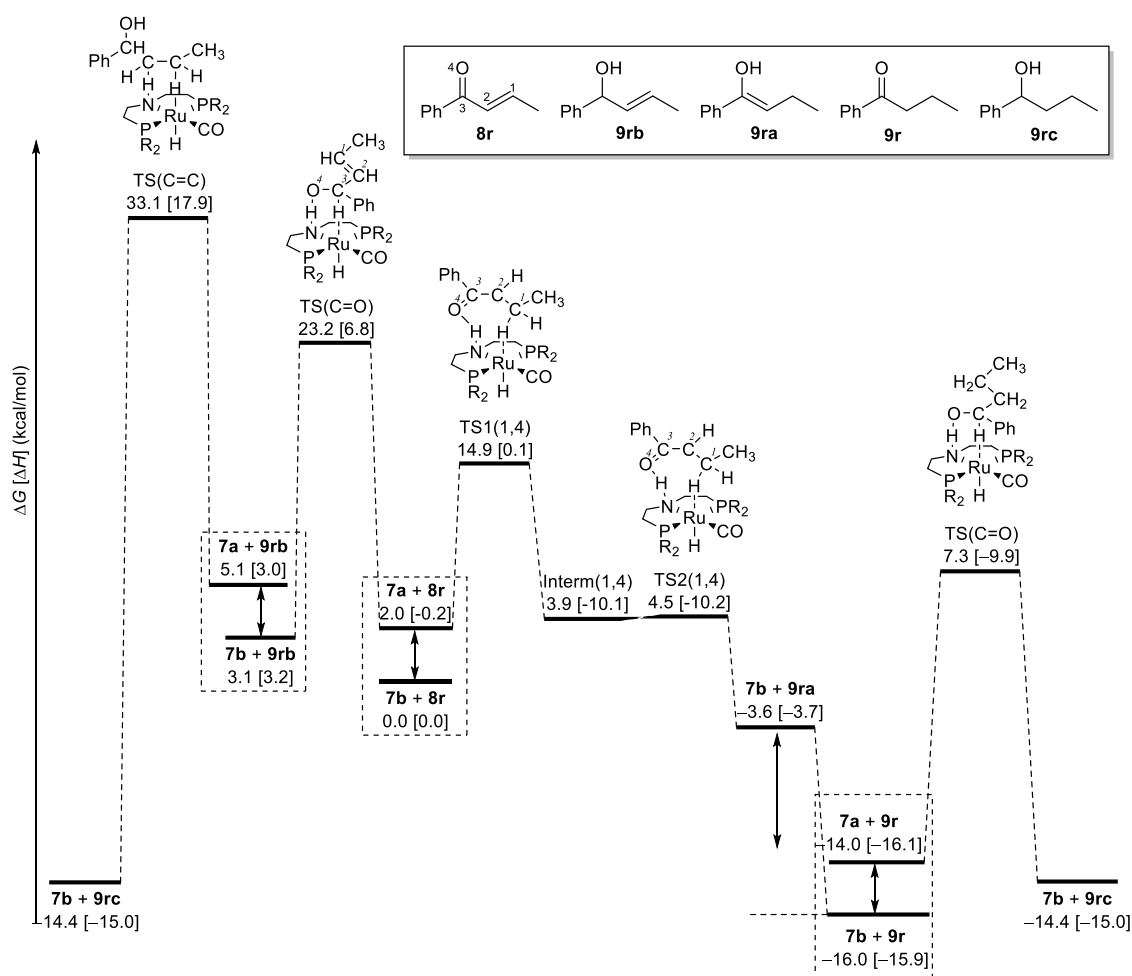
the light of these results it is clear that the selectivity achieved experimentally towards C=O reduction is a consequence of kinetic control of the reaction since the difference between the pathways C and B is only 1.4 k/cal mol and the formation of butyraldehyde and butanol are thermodynamically favoured. It is noticeable that the barriers for *i*PrOH dehydrogenation to acetone are higher than the ones described for substrate transformation. Therefore, it should be this dehydrogenation process that is the rate determining step which driving force relies on two factors: 1, the highly volatility of acetone (53 °C boiling point) at the *i*PrOH reflux temperature (83 °C boiling point) and 2, the large excess of hydrogen source used. When EtOH is used, the formation of 2 molecules of crotyl alcohol requires 2 consecutive dehydrogenations. The first



Scheme 7. Potential energy surface of croton aldehyde (8a) hydrogenation using *i*-PrOH as hydrogen source

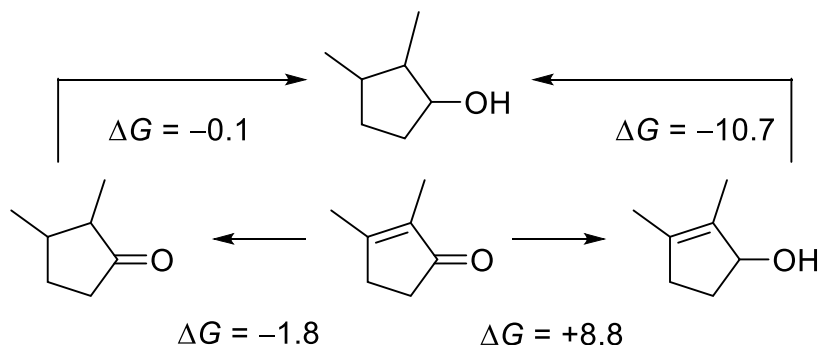
one, the dehydrogenation of 1 molecule of EtOH to acetaldehyde which further reacts with another molecule of ethanol forming the hemiacetal. Next, the hemiacetal undergoes the second dehydrogenation and releases 1 molecule of ethyl acetate as observed experimentally. This transformation is exergonic by 3.03 Kcal/mol, thus is a thermodynamically favoured process. Ethyl acetate (77.1 °C boiling point) is also slightly more volatile than EOH at reflux temperature (78 °C boiling point). However when cyclohexanol (161,8 °C boiling point) was successful used as hydrogen source at 90°C forming cyclohexanone as by-product (155.6 boiling point) (Table 2, entry 8) then, should be the case that the main driving force is the excess of *i*PrOH. EtOH or cyclohexanol depending on the case.

In order to explain the reversed selectivity observed when (*E*)-1-phenylbut-2-en-1-one was submitted to the base free TH (Table 3, entry 1), surface energies of the corresponding pathways were calculated (Scheme 8). In contrast to what was seen for croton aldehyde, the pathway C is more hindered than the pathways A and B. Indeed, whereas the pathway C has a Gibbs free energy barrier of 21.2 kcal and is endergonic by 1.1 Kcal/mol, the B pathway which leads to the enol formation is exergonic by 5.6 Kcal/mol and has a free energy barrier of 12.9 Kcal/mol for the hydride transfer followed by another free energy barrier of 2.5 cal/mol for the proton transfer. In addition, tautomerization to the saturated ketone is exergonic by 12.4 Kcal/mol. Optimizations of the TS for the pathway A always led to the pathway B. Analogously to what happens with crotyl alcohol, 1-phenylbut-2-en-1-ol cannot be easily further hydrogenated to 1-phenylbutan-1-ol because the process has an energy barrier of 28.0 Kcal/mol in spite of the favoured thermodynamics. Indeed, the process is as exergonic by 19.5 Kcal/mol. These differences in the energy barriers between the pathways B and C when croton aldehyde and 1-phenylbut-2-en-1-one are likely to be a consequence of the phenyl ring that substrate **8r** is bearing which is causing steric hindrance, therefore increasing the energy barriers for the TS for the C pathway. Is noticeable that as happened with the starting material, the pathway C for the saturated ketone which also leads to 1-phenylbutan-1-ol has a high energy barrier of 21.3 Kcal/mol and the reaction is exergonic by 0.4 Kcal/mol. In conclusion, in this case 1-



Scheme 8. Potential energy surface of (*E*)-1-phenylbut-2-en-1-one (**8r**) hydrogenation using iPrOH as hydrogen source.

phenylbutan-1-one is shown to be both the kinetic and the thermodynamic product. This is in agreement with the experimental results. Since the pathway B has a lower energy barrier than the one for iPrOH dehydrogenation it is clear that the latter one is the rate determining step similar as for the croton aldehyde TH. Finally, in order to explain why *cis*-Jasmone and 2,3-dimethyl-cyclopent-2-en-1-one remained completely unreactive under our TH protocol (Table 3, entry 19), thermodynamic calculations on the TH of 2,3-dimethyl-cyclopent-2-en-1-one were also performed (Scheme 9). The pathway C for the C=O reduction is not favoured



Scheme 9. Computed thermodynamics (kcal/mol) of the reduction of 2,3-dimethylcyclopent-2-en-1-one

thermodynamically. In fact, the reduction is endergonic by 8.8 Kcal/mol under our TH protocol. This explains why allylic alcohol was not obtained. The pathway A which allows the C=C double bond hydrogenation is slightly exergonic by 1.8 Kcal/mol. However, the energy barriers of the TS of this pathway is expected to be very high because the steric hindrance caused by 4 substituents on the olefin. Thus, this pathway is likely to be kinetically hindered.

2.2.4. Conclusions and further prospects

Conclusions

- Readily commercially available PNP complex Ru-MACHOTM-BH was shown to be a very active and selective catalyst for the transfer hydrogenation of aromatic and aliphatic aldehydes and ketones and α,β -unsaturated carbonyl compounds using EtOH or iPrOH as hydrogen donors.
- An outer sphere mechanism was postulated as a plausible mechanism and B3PW91 density functional theory computations were performed. The results match with bifunctional catalysis in an outer sphere mechanism and using crotonaldehyde as a model compound the selectivity towards allylic alcohols could be rationalized as a consequence of the kinetic control of the reaction. When the carbonyl moiety is sterically hindered, the selectivity is reversed towards C=C double bond hydrogenation since saturated carbonyl compound turn out to be both the kinetic and the thermodynamic product as was calculated using (*E*)-1-phenylbut-2-en-1-one as representative example.

Further prospects

- Further research on catalysts capable of dehydrogenating ethanol to acetaldehyde is highly desired. So far, in the dehydrogenation of alcohols to aldehydes in the liquid phase using homogeneous catalysts only traces of the corresponding aldehyde were detected when heptanol was used as substrate in presence of Fe-MACHO-BH complex for the coupling of primary alcohols to esters.^[51]
- Finally, in order to further develop green chemistry with the aim of reducing the impact on the environment from chemical processes, research will be needed on replacing precious metals with other more abundantly available metals like Mn, Fe, Co or Ni and on replacing phosphorous based ligands with other less harmful systems but maintaining activity and selectivity.

2.3. Chapter 2. Base-free Iron-catalysed transfer hydrogenation of esters using EtOH as hydrogen source.

2.3.1. Introduction. State of the art.

A different challenge in the TH field is the reduction of ester functionalities. Many examples exist in the literature for the reduction of this functional group using H₂ gas.^[38b, 52] However, despite the increasing amount of publications in the last decade on the TH of ketones and imines, the TH of the more demanding esters remains scarce.^[9d] In fact, only 2 Ru based catalysts have been reported to be active for the TH of ester groups (Figure 1).^[53] The proof of concept was reported for the first time by Nikonov in 2015.^[53a] He and his group prepared a range of half sandwich ruthenium-based complexes capable of reducing ketones, nitriles and ester functionalities. However, only activated esters like trifluoroacetates were converted to the

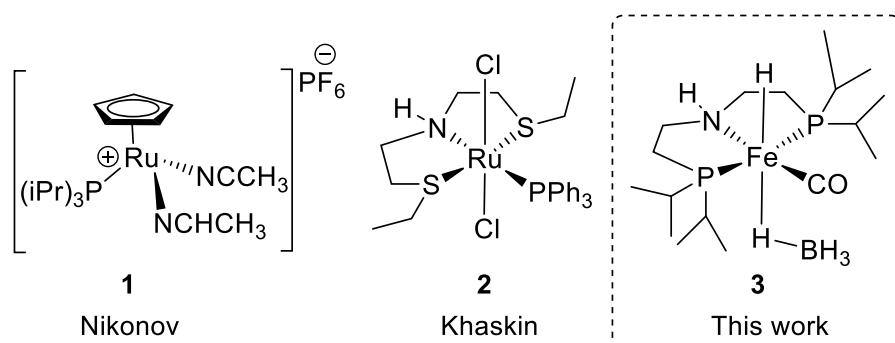


Figure 1. Catalysts used in the transfer hydrogenation of esters.

corresponding alcohols with up to 60% yields. One of the biggest problems he encountered was the trans-esterification with iPrOH, which led to the more sterically hindered isopropyl esters which were reduced much slower. The following year, Khaskin and his group reported an ester metathesis protocol using the Ru based Gusev catalyst.^[53b] Interestingly, they envisioned the possibility of using this reactivity for the transfer hydrogenation of esters. Indeed, using catalyst **2** in combination with tBuOK and EtOH as H₂ source in toluene at 80 °C during 16 hours allowed the reductions of aliphatic and aromatic esters, lactones and triglycerides. Also they observed that EtOH behaved better as hydrogen donor than iPrOH. Worth of highlighting is the good tolerance of the catalyst to pyridine and tertiary amine moieties. Nevertheless, we believe there is room for improvement of this otherwise interesting methodology. First of all, it is highly desirable to replace precious metals with earth abundant metals. Secondly, it would be highly desirable as well to avoid the use of bases in order to expand the scope to substrates which are unstable in basic media. PNP Fe catalyst **3**, also known as Fe-MACHO-BH, is a well-known catalyst for a number of processes and transformations which include production of hydrogen via the dehydrogenation of alcohols and the reduction of a large number of other functionalities using H₂ gas.^[54] Because of these reports we thought that Fe-MACHO-BH could possibly be an excellent candidate for the base-free TH of esters.

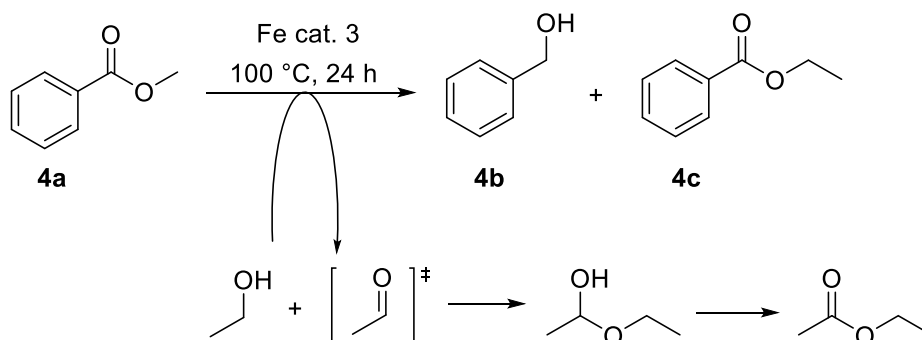
2.3.2. Objectives

- Synthesis of Fe-MACHO-BH according to the described procedures and testing the condition for the optimization of the transfer hydrogenation of ester containing compounds.
- Exploration of the scope and limitations with regard to differently substituted esters and other functionalities.
- Comparison of the activity of Fe-MACHO-BH with the commercially available Ru analogue and the previously synthesized Mn analogue in the base-free transfer hydrogenation of ester compounds.

2.3.3. Results and discussion

2.3.3.1. Preliminary experiments

In the first experiment, benzoic acid methyl ester was dissolved in a large excess of EtOH and stirred for 24 hours at 100 °C in the presence of 5 mol% of Fe-MACHO-BH (**3**). After that time we were delighted to see the full conversion of the starting material and an 88% GC yield of benzyl alcohol **4b** (Table 1, entry 1). The rest of the substrate was converted into ethyl benzoate **4c** with 10% GC yield via trans-esterification of the starting material and the solvent. As was seen in the previous chapter, ethyl acetate was detected by GC-MS as a consequence of the hemiacetal formation with 1 molecule of acetaldehyde and 1 molecule of EtOH followed by its dehydrogenation (Scheme 1).



Scheme 1. Base-free based transfer hydrogenation of methyl benzoate (**4a**) using Fe-MACHO-BH. Preliminary experiment.

2.3.3.2. Optimization of the Reaction Conditions

Next, we tested different hydrogen sources for comparison. Similar to Nikonov's results, the use of secondary alcohol (iPrOH) as a hydrogen source only yielded 56% of benzyl alcohol (Table 1 entry 3). The transesterification issue could be solved in principle by using MeOH as hydrogen donor. However, when MeOH was used, none of the desired product was formed even when a base was added (Table 1, entry 2). When a mixture of MeOH:EtOH (1:1) was used, the desired reaction did not occur. If 2.5 eq. of MeOH with respect to substrate were added to the reaction the yield of benzyl alcohol **4b** increased to 61% GC yield (Table 1, entry 4). These results suggest that MeOH is poisoning the catalyst and EtOH clearly is the most suitable hydrogen source for the base free TH of esters out of the three alcohols that were tested. After that,

Table 1. Screening of alcohols as the reducing agents for the base-free transfer hydrogenation of esters.^a

4a 4b 4c

Entry	Cat. Load. [mol%]	Hydrogen Source	Conv. [%]	Yield of 4b [%]	Yield of 4c [%]
1	5	EtOH	>99	88	10
2 ^b	5	MeOH	7	0	0
3	5	iPrOH	95	56	39
4	3	EtOH/MeOH ^c	98	61	35
5	3	EtOH/MeOH ^d	41	1	36

^aReaction conditions: Substrate (0.5 mmol), alcohol (96 eq.), catalyst **3** (5 mol%), 100 °C, 24 hours, conversion and yield determined by GC using dodecane as an internal standard. ^b25 mol% of t-BuOK was added. ^c2.5 eq. of MeOH with respect to the substrate were added. ^d96 eq. of MeOH with respect to the substrate were added.

optimization of the reaction conditions was performed and the results are summarized in Table 2. At first, the catalyst loading was reduced to 4 mol%, however only 64% CG yield of the desired alcohol was obtained (Table 2, entry 2). Yields were also decreasing when the number of EtOH eq. was changed (Table 2, entries 3-4). The influence of the temperature was also studied. At 80 °C the results turn out to be almost the same and 87% yield of the product was obtained (Table 2, entry 5). However, lowering it to 60 °C reduced the yield significantly to 40% (Table 2, entry 6). Thus, the standard conditions were defined as 96 eq. of EtOH as the hydrogen source, 5 mol% of Fe cat. **3**, 100 °C and 24 hours reaction time (Table 2, entry 1).

Table 2. Optimization of the reaction conditions.^a

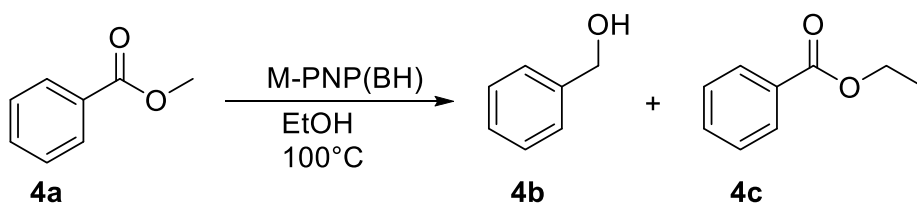
4a 4b 4c

Entry	Cat. Load. [%mol]	EtOH [eq.]	Temp. [°C]	Conv. [%]	Yield of 4b [%]	Yield of 4c [%]
1	5	96	100	>99	88	10
2	4	96	100	>99	64	29
3	5	120	100	>99	74	21
4	5	45	100	>99	78	21
5	5	96	80	>99	87	13
6	5	96	60	>99	40	59

^aReaction conditions: substrate (0.5 mmol), catalyst **3**, 100°C, 24 hours, conversion and yield determined by GC using dodecane as an internal standard.

2.3.3.3. Kinetic profile of the Fe(MACHO)-BH catalysed transfer hydrogenation of methyl benzoate. A comparison of Fe to Ru and Mn.

At this point of the project achieving higher selectivities was desired. In order to understand better the driving forces of the reaction, monitoring of the TH of methyl benzoate catalysed by the Fe catalyst and its Ru and Mn analogues were performed (Scheme 2, Figures 2,3).



Scheme 2. General scheme for the monitorings of the metal catalysed TH of Methyl benzoate (**4a**) to benzyl alcohol (**4b**) 4b using EtOH as H₂ donor.

When the reaction was run using Fe catalyst **3** the fastest transformation was seen to be the transesterification of starting material to ethyl benzoate (**4c**). However, reduction of the carbonyl moiety of both the ethyl ester and the methyl ester to benzyl alcohol (**4b**) was also observed. Noticeable, only 7 hours were required to achieve a steady state. This result suggests a possible existence of an equilibrium governing the reaction. Although ethyl benzoate is initially rapidly

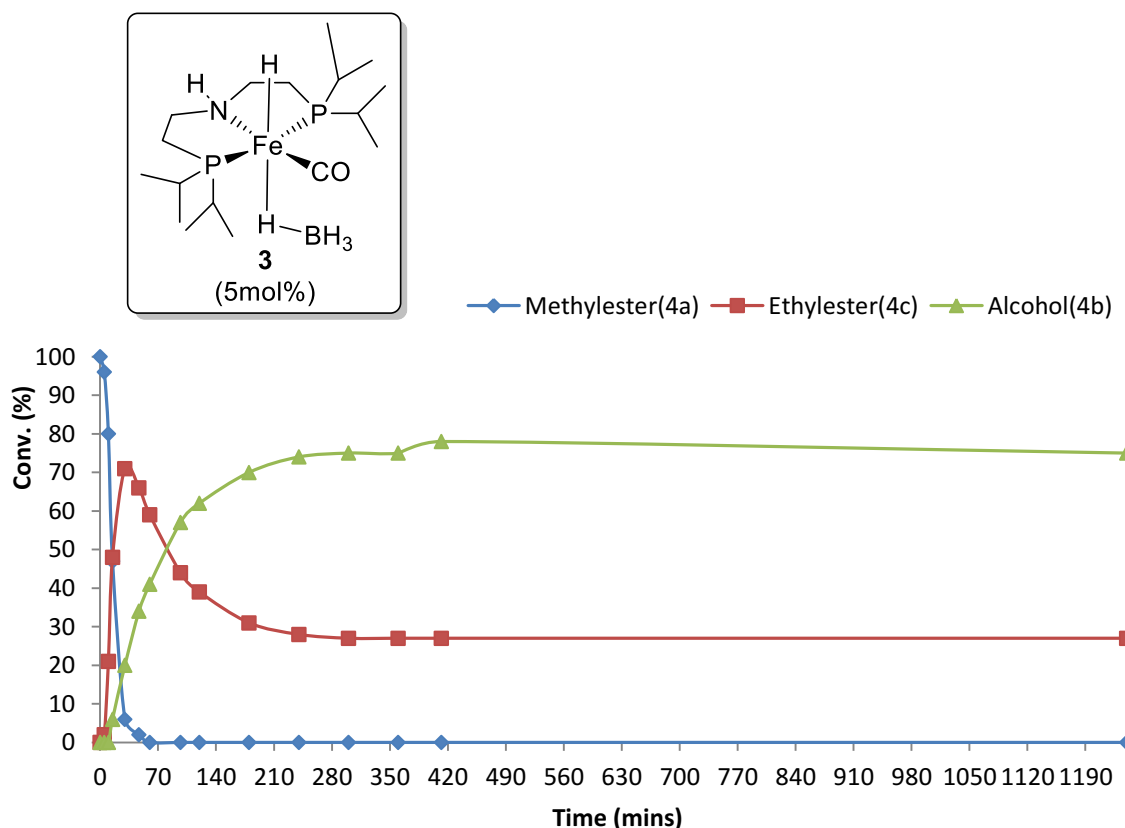
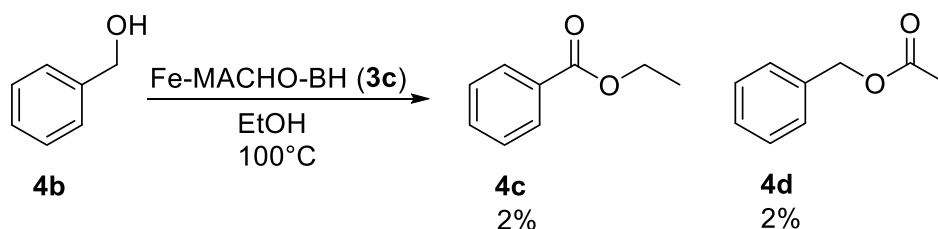


Figure 2. . Monitoring of the Fe catalysed TH of Methyl benzoate (**4a**) 4a to benzyl alcohol (**4b**) 4b using EtOH as H₂ donor.



Scheme 3. Reaction scheme of the reverse reaction of TH of esters using Fe catalyst **3c**.

formed via trans-esterification it can also be formed via the dehydrogenation of benzyl alcohol to benzaldehyde followed by the coupling of one molecule of ethanol and further dehydrogenation of the acetal to ethyl benzoate (**4c**). This would establish an equilibrium between benzyl alcohol and ethyl benzoate. In order to prove this possibility, benzyl alcohol (**4b**) was reacted under the defined standard conditions. This resulted in 2% GC yield of both ethyl benzoate (**4c**) and benzyl acetate (**4d**) proving feasible the reverse reaction (Scheme 3). Next, monitoring of the TH of methyl benzoate (**4a**) using EtOH as H₂ source catalysed by commercially available Ru-MACHOTM-BH^[37] was performed for comparison (Figure 3).

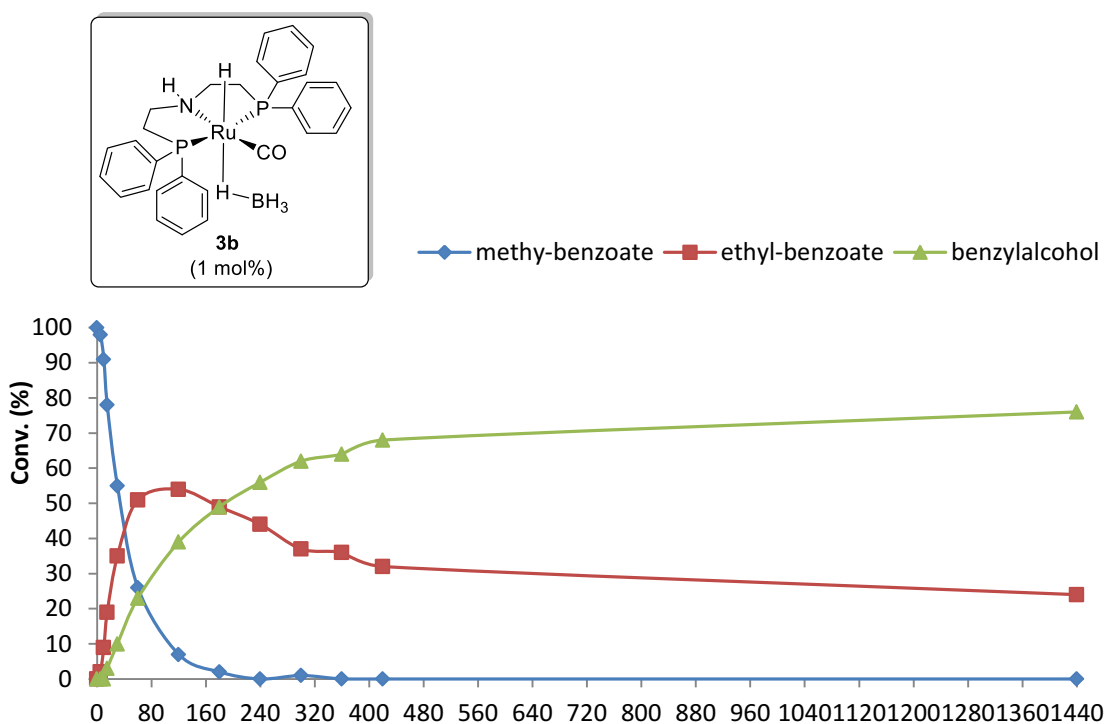
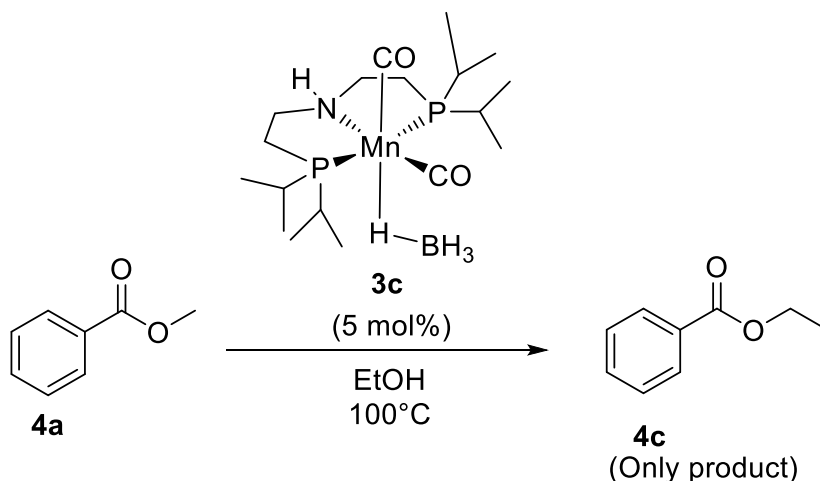


Figure 3. Monitoring of the TH of the Ru catalysed TH of Methyl benzoate (**4a**) to benzyl alcohol (**4b**) using EtOH as H₂ donor.

Interestingly, the results from the Ru catalysed TH of esters were supporting the postulated equilibrium between EtOH, benzyl alcohol (**4b**) and ethyl benzoate (**4c**). Indeed, the final ratio of 3:1 between benzyl alcohol and ethyl benzoate was the same in both Fe and Ru catalysed reactions after 7 hours. Because of the higher catalyst loading that was required in the hydrogenation step, when Fe catalyst **3** was used, the previous transesterification step was much faster in the Fe-catalysed reaction (Figure 2). Due to steric hindrance, the hydrogenation of ethyl benzoate is slower than its methyl counterpart. This is the first time that Ru-MACHOTM-BH is

shown to be active for the base-free transfer hydrogenation of esters. Finally, Mn-MACHO-BH was synthesized according to the previously reported procedure^[55] and tested for the TH of methyl benzoate using the defined protocol. However, in this case in addition to the expected ethyl acetate, only transesterification was observed (Scheme 4). This result fits with the reported lower activity of Mn based complexes for hydrogenation of esters in comparison with its Fe and Ru counterparts.



Scheme 4. Reaction scheme of the results for the TH of methyl benzoate catalysed by Mn catalyst **3c**.

2.3.3.4. Scope and limitations

At this point, an exploration of the scope and limitations of the system were done using the defined conditions described in section 2.3.3.2. A large variety of aromatic esters were reduced to the desired alcohols (Table 3). When non-substituted aromatic esters were used as substrates, the corresponding alcohols were easily obtained with isolated yields of up to 86% (Table 3, entries 1-3). A quantitative alcohol yield was obtained with heteroaromatic ester **16a** (Table 3, entry 7). When a substrate contains two different carbonyl moieties like compound **7a**, both groups were reduced affording the corresponding diol **7b** in 80% isolated yield. Even better yields were obtained when the methyl benzoates were substituted in the *para* position with a fluorine (**8a**) or chlorine (**9a**) atom giving 98% and >99% isolated yields respectively (Table 3, entries 9-10). Proving the robustness of the process, when the reaction was scaled up 10 times using substrate **9a**, no significant loss in the isolated yield was observed. Indeed, a 95% isolated yield of the desired alcohol **9b** was achieved (Table 3, entry 10[f]). However, when the methyl benzoate was bearing a bromine atom in the *para*- position, only 14% GC-Yield was achieved (Table 3, entry 11). In the same way, *para*-nitro benzoate **11a** did not show any conversion (Table 3, entry 12). Also, when the aromatic ring was substituted with different amines (compounds **12a** and **13a**), no conversion of the starting material was detected (Table 3, entry 12). Likewise, other ester compounds bearing other nitrogen based functional groups like azides, nitriles and amides were totally inactive. A plausible explanation for the lack of activity with this substrate could be the propensity of the nitrogen atom to bind to the Fe atom centre, thereby poisoning the catalyst. This cannot be the correct explanation for the lack of reactivity of the *p*-nitrobenzoate. The lack of activity of this substrate is possibly due to the strongly acidic character of the corresponding alcohol caused by the NO₂ group which binds to the iron.

Table 3. Aromatic substrate scope of the Fe-MACHO-BH catalysed transfer hydrogenation of ester compounds.^a

Reaction scheme: $\text{R}^1\text{-C}_6\text{H}_4\text{-C(=O)OR}^2 \xrightarrow[\text{EtOH (96 eq.)}]{\text{Fe catalyst 3 (5\%mol)}} \text{R}^1\text{-C}_6\text{H}_4\text{-CH}_2\text{OH}$

Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1			73	7			>99
2			77	8			80 ^c
3			84 ^b	9			98
4			71 ^b	10			>99 95 ^f
5			>99 ^c	11			14 ^g
6			86 ^d	12		No new product	
					11a, X = O 12a, X = H 13a, X = Me		

^aReaction conditions: substrate (0.5 mmol), 96 eq. of EtOH (2800 μL), Fe catalyst **3** (5 mol%, 9.7 mg), 100°C, 24 hours reaction time in a pressure tube covered from light. All yields are isolated unless mentioned otherwise. ^bYield corresponds to saturated alcohol. ^cMn catalyst **3c** (5 mol%) was used. The product is ethyl 3-(p-methoxyphenyl)propanoate. ^dYield is calculated by dividing the amount of benzyl alcohol by 2. ^eSubstrate (0.21 mmol), EtOH 120 eq. (2100 μL). 2.5 mol% of Fe cat **3** was added extra. ^fReaction conditions: substrate 5 mmol, 96 eq. of EtOH 96 (27 mL), Fe catalyst **3** (5 mol%, 97.5 mg). ^gYield determined by GC.

On the other hand, other aromatic compounds like α,β -unsaturated esters **14a** and **15a** gave better yields. However, the C=C double bond was also reduced in the reaction affording the saturated alcohols in 84% and 71% isolated yields, respectively (Table 3, entries 3-4). Mn-

MACHO-BH (**3c**) was also tested for the TH of α,β -unsaturated carbonyl compound **15a** for comparison. In this case, absolute selectivity to the saturated trans-esterification ester **15c** was observed (Table 3, entry 5). Reduction of C=C double bonds and C \equiv C triple bonds in a homogeneous catalysed TH processes using 1st row metals has been done before with manganese-,^[56] iron-,^[57] cobalt-,^[58] and nickel-based^[59] catalysts. However, most of these complexes required different hydrogen donors than alcohols, as well as a base as additive. Therefore, this experiment represents the very first example of the base-free Mn-catalysed TH of activated olefins using EtOH as hydrogen donor. Next, aliphatic esters were tested. We were delighted to see that this type of substrate was also reduced with good yields using the same protocol (Table 4). As a representative example, the system allowed to convert methyl hexanoate (**17a**) to 1-hexanol (**17b**) with 77% isolated yield (Table 4, entry 1). In regard to the development of renewable processes, the relevance of compounds such as adipic acid dimethyl ester, methyl oleate and methyl levulinate is well-documented^[2a-d, 2f-h] Because of their potential

Table 4. Aliphatic substrate scope of the Fe-MACHO-BH catalysed transfer hydrogenation of ester compounds.^a

Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1			77	5			63 ^c
2			97 ^b	6			99 ^d
3			92 ^c	7			87 ^e
4			53 ^c				

^aReaction conditions: substrate (0.5 mmol), 96 eq. of EtOH (2800 μ L), Fe catalyst **3** (5 mol%, 9.7 mg), 100 $^{\circ}$ C, 24 hours reaction time in a pressure tube covered from light. All yields are isolated unless mentioned otherwise. ^b2.5 mol% of cat **3** extra was added. ^cYield corresponds to unsaturated alcohol. ^d5 mol% of cat **3** per eq. of ester moiety and 123 eq. of EtOH (3600 μ L) were used. ^eSubstrate (0.25 mmol of basic unit of the polymer), 5 mol% of cat **3** per eq. of ester moiety is used.

as platform chemicals, these compounds attracted the attention of many research groups in both academia and industry. Nevertheless, only a few catalytic systems were reported to afford 1,4-pentandiol (**18b**) from methyl levulinate (**18a**) in a selective fashion.^[60] Gratifyingly, our protocol allowed almost quantitative conversion of methyl levulinate (**18a**) into 1,4-pentandiol (**18b**) (Table 4, entry 2). Furthermore, adipic acid dimethyl ester (**22a**) afforded 1,6-hexandiol with 99% isolated yield (Table 4, entry 3). And methyl oleate (**19a**) gave the desired unsaturated alcohol in 92% yield. Noticeably, non-conjugated C=C double bonds remained intact under the reaction conditions (Table 4, entries 3-5). Another interesting topic in renewable chemistry is the recycling of polymers. One way of doing this is to reconvert them to their monomers.^[61] Due to the exponential growth of plastic use in industry, accumulation of waste from polymers has become a significant problem for the environment. Many research groups are currently working on polymer recycling chemistry,^[62] however, there are still challenges to overcome. For instance, designing catalysts that are efficient for the depolymerisation of different polymers with high selectivities, high turnover numbers and high rates has become the main focus of different research groups.^[63] Only 3 examples of the use of homogeneous catalysts for polyester deconstruction to monomeric diols were reported, in all cases this was achieved via ruthenium based hydrogenation reactions.^[64] To the best of our knowledge there are no reports in the literature on polyester reduction to the corresponding diols using a TH process. The registered polyester Dynacol 7360 (**23a**) consists of chains of alternating adipic acid and 1,6-hexandiol units. To our delight, 1,6-hexandiol was obtained in 87% isolated yield when this polymer was treated under our defined standard conditions. This result represents a completely new strategy for recycling polyesters by smoothly reducing them into their basic units for further applications. Next, we examined the hydrogenation of lactones. Lactones are widely used in the fragrance and flavour industries.^[65] This type of substrates was also reduced using our protocol (Table 5). The corresponding diols from 6- and 7- membered lactones were easily obtained in high yields when substrates were treated with our defined base-free conditions (Table 5, entries 1-2). Another renewable bio-based compound which can be obtained from sugars via the ring-closure of levulinic acid is α -Angelica lactone (**26a**). When this 5-membered ring lactone was used as the substrate, the saturated lactone was observed as the only product (Table 5, entry 3). Surprisingly, it was found that addition of 25 mol% of NaOEt to the reaction resulted in complete reduction to the diol. In that way, α -Angelica lactone (**26a**) and whiskey lactone (**27a**) were reduced to the corresponding diols with >99% and 70% isolated yield respectively (Table 5, entries 4-5). It is well known that the equilibrium between the hydroxyl ester produced from the alcoholysis of the lactone and the 5-membered ring lactone is completely shifted to the lactone. Nevertheless, in the light of our results we are inclined to think the presence of the base allows the ring opening of the lactones to the hydroxyl ester compounds which will be then reduced to corresponding diol. A different explanation was recently reported by Milstein when studying a cobalt based system for the hydrogenation of ester compounds. They proposed a mechanism involving the hydrogenation of the double bond of the enolate.^[66]

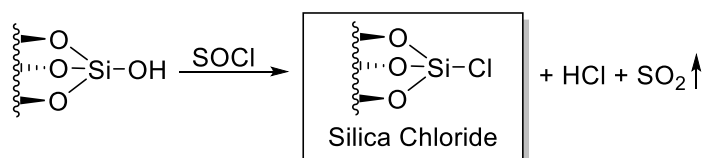
Table 5. Lactone substrates scope of the Fe-MACHO-BH catalysed transfer hydrogenation of ester compounds.^a

Reaction scheme: Lactone **a** (with R group) reacts with Fe catalyst **3** (5%mol) in EtOH (96 eq.) at 100 °C, 24 h to form diol **b**.

Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1			>99 ^b	4			>99 ^c
2			89	5			70 ^c
3			>99 ^b				

^a Reaction conditions: substrate (0.5 mmol), 96 eq. of EtOH (2800 μ L), Fe catalyst **3** (5 mol%, 9.7 mg), 100 °C, 24 hours reaction time in a pressure tube covered from light. All yields are isolated unless mentioned otherwise.^b Yield is based on the single peaks observed by GC and products were characterized by GC-MS. ^c 25 mol% of EtONa was used

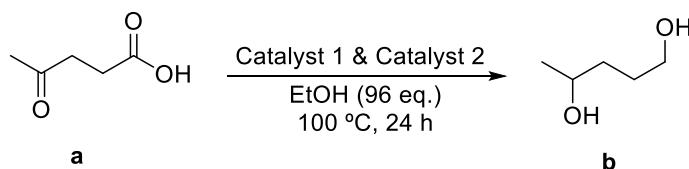
Finally, carboxylic acids were also tested under our reaction conditions. However, when levulinic acid was treated with our protocol, a mixture of products was obtained, none of which were the desired diol. Then, we envisioned a possible tandem reaction in which esterification of the carboxylic acid occurs followed by the already reported TH. This would afford the corresponding alcohol from the acids. Several mixtures of different catalysts or catalyst/additive combinations including homogeneous/heterogeneous ones were attempted for the reduction of levulinic acid (Table 6). When different Lewis acids were combined with Ru or Fe PNP complexes, only complicated mixtures of products were observed (Table 6, entries 1-4). SiOCl is a heterogeneous catalyst which is used for different transformations including esterification of carboxylic acids to esters in the presence of excess of EtO^[67] This catalyst is basically a silica gel where some OH groups on the surface are substituted by chloride atoms (Scheme 5).



Scheme 5. Schematic synthesis of SiOCl

After synthesizing SiOCl according to the literature procedure,^[67b] combinations of Ru or Fe MACHO-BH complexes with SiOCl were tested in the TH of carboxylic acids. After 24 hours reaction, full conversion to a large variety of compounds was observed. In this mixture, only traces of the desired diol were observed.

Table 6. Tandem approach for the TH of Levulinic.^a



	Catalyst 1	Catalyst 2	Diol observed
1	Al(<i>i</i> PrO) ₃ ^b	Fe-MACHO-BH	No
2	Al(<i>i</i> PrO) ₃ ^b	Ru-MACHO TM -BH	No
3	BF ₃ ·Et ₂ O ^b	Fe-MACHO-BH	No
4	BF ₃ ·Et ₂ O ^b	Ru-MACHO TM -BH	No
5	SiOCl ^c	Fe-MACHO-BH	Traces
6	SiOCl ^c	Ru-MACHO TM -BH	Traces

^aReaction conditions: substrate (0.5 mmol), 96 eq. of EtOH (2800 μ L), catalyst 2 (5 mol%) 100°C, 24 hours reaction time in a pressure tube covered from light. ^b10 mol% of catalyst 1 was used. ^c40 mol% of catalyst 1 was used.

2.3.4. Conclusions and further prospects

Conclusions

- A completely new strategy was developed for the reduction of esters via Fe-catalysed base-free transfer hydrogenation using EtOH as hydrogen source and solvent.
- Under our protocol, a broad scope of aromatic and aliphatic esters as well as lactones, was reduced to corresponding alcohols. Remarkably, important substrates from the renewable chemistry point of view, such as α -Angelica lactone, methyl oleate and adipic acid dimethyl ester were also reduced.
- Renewable methyl levulinate was reduced to 1,4-pentandiol in a single pot reaction.
- A polyester was depolymerized to the corresponding diol using a transfer hydrogenation process for the very first time. This represents a completely new strategy in plastic recycling which may be useful in the future.
- All substrates containing nitrogen based functional groups like NO₂, amines, nitriles and azides did not undergo TH of the ester moiety. In addition, levulinic acid was also unreactive even when different Lewis acids were used as co-catalysts.
- Ru-MACHOTM-BH was shown to be active for the base-free transfer hydrogenation of methyl-benzoate using EtOH as H₂ source and solvent.
- For the first time a Mn-based catalyst was used for the base-free transfer hydrogenation of methyl 3-(4-methoxyphenyl)prop-2-en-oate to ethyl 3-(4-methoxyphenyl)propanoate using EtOH as H₂ source and solvent.

Further prospects

- Explore the limits of the protocol in depolymerisation of a broader scope of polymers like other polyesters and polycarbonates via transfer hydrogenation protocols which are already in process in other research groups.
- Further research on finding catalysts which allow higher activity and tolerates nitrogen based functionalities will be highly desired. In addition, future work on the development of catalysts capable of selective reduction towards the carbonyl moiety in α,β -unsaturated esters is also very interesting.
- Designing systems which enable the transfer hydrogenation of carboxylic acids would be very interesting for renewable chemistry as it would reduce the number of steps required for obtaining diols from renewable compounds.
- Replacement of phosphine based ligands by other phosphine free ligands is in demand for greener and cheaper processes.
- Optimize conditions and explore the scope of the Base-free transfer hydrogenation of C=C and C \equiv C bonds using alcohols as H₂ source and Mn-MACHO-BH as catalyst is currently under development in the group.

3. Chapter 3. Exploration of Rh single atom catalysis for new chemical transformations.

3.1. Introduction

3.1.1. Single atom catalysts (SAC)^[68]

In most large-scale chemical processes in industry, catalysis plays a crucial role. For that reason, improving and optimizing the currently used catalysts and the development of new ones is a fundamental priority. Considering homogeneous catalysis, it is well-established that the development of organometallic complexes with a defined structure bearing carefully designed ligands, which may contain different metallic centres, allows us to perform many different chemical transformations under mild conditions with unique selectivity. However, homogeneous catalysts tend to be unstable at high temperatures which reduces the total turnover number. Heterogeneous catalysts on the other hand can handle much higher temperatures but are less reactive and selective. Another drawback of heterogeneous catalysts is the intrinsic difficulty of identifying the real catalytic species and the intermediates on the catalytic pathway. Thus, determining the mechanism of the catalytic reaction is much harder than with homogeneous catalysis. Furthermore, because metal present is mainly in the form of large aggregates, catalysis can take place only on the outer sphere metal atoms and the metals in the core of these particles are “wasted”. This, of course, increases the overall costs. Therefore, systems that possess both the robustness of the heterogeneous catalysts, and the possibility for high selectivity by fine-tuning of the catalyst as in homogeneous catalysis are highly desirable. Attempts to achieve this goal led to the blossoming of nanoparticles science for catalysis.^[69] In this field, tuning the surface area and the morphology of the (supported) nanoparticles is

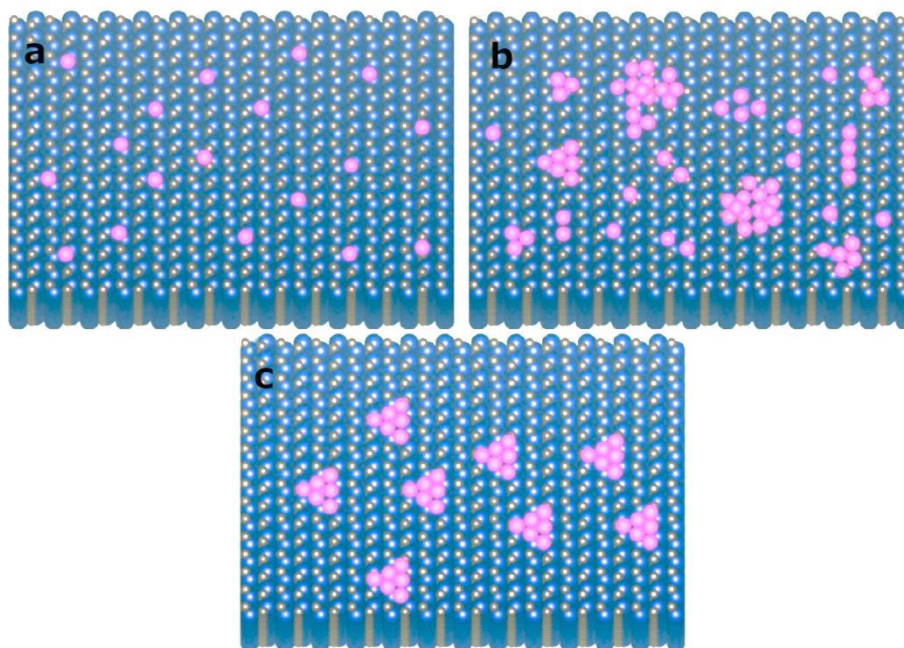


Figure 1. Schematic representations of the different dispersion modes for metal atoms on the support. a) Single atom catalyst (SAC) also known as heterogeneous single-metal site catalyst (HSMSC). b) Atomically dispersed supported metal catalyst (ADSMC). c) Single site heterogeneous catalyst (SSHC).

approached by rational design, leading to major improvements in activity and selectivity for different reactions. However, nanoparticles still contain “wasted” metal atoms in the core of the particles, which furthermore, behave different to the ones on the surface concerning chemical activity. Thus mechanistic studies still remain complicated. In the last 10 years, reducing the size of the supported particles to only a single atom opened a completely new field in catalysis. These catalysts possess new and unique features which in many cases imparts properties that are totally different from those of the nanoparticles.^[68b] Nevertheless, these differences do not always lead to higher rates but rather to different reactivities and selectivities. The most appealing characteristics of this type of new catalysts, known as single atom catalysts (SAC), (Figure 1, a) is the complete use of all metal atoms present on the support. Due to the critical role that the support plays in the catalytic activity, SAC’s are also referred to in the literature as heterogeneous single-metal site catalysts (HSMSC).^[68c] It should be mentioned that there are other types of metal aggregates in which the access to the metal atoms also corresponds to 100%. However, their distribution on the support is slightly different. For that reason, they are referred to by different names as shown schematically in Figure 1.^[68a] Single site heterogeneous catalysts (SSHC) (Figure 1, c), these catalysts ensembles contain more than one atom but they are isolated from one another in space and all atoms are on the surface of the aggregate. Atomically dispersed supported metal catalyst (ADSMC)(Figure 1, b), in this type, the size of the metallic sites can differ in the number of atoms from a single atom to small clusters and all coexist at the same time in the catalyst. SACs can be considered as the simplest sub-type of both the SSHC and ADSMC families. Finally, there is another type known as Site-Isolated Heterogeneous Catalysts (SIHC), this term refers to catalyst that contain anchored organometallic complexes, distributed homogeneously on the surface, therefore the metal centre is protected by a ligand. However, in spite of years of work on this type of catalysts they have not yet been used in industry.^[70] There are practical applications for SACs in the most chemical transformations. Such transformations include but are not limited to hydrogenations, oxidations, reforming and cross-coupling reactions, electro-catalysis and photo-catalysis.

3.1.2. State of the art in Rh single site catalysts ^[71]

Due to the extensively reported use of rhodium in both homogeneous and heterogeneous catalysis,^[72] isolating Rh atoms on different supports to study the prospective new properties of Rh single site catalysts has caught the interest of many research groups in the last 5 years. The very first literature report on the isolation and use of Rh single atoms was in 1979 when Vaughan dispersed Rh atoms on Al₂O₃ and used these for the catalytic decomposition of formaldehyde, which led to the formation of supported and isolated rhodium carbonyl hydride species.^[71a] After that, possibly due to the lack of tools for characterizing the catalysts, no reports appeared on the synthesis and use of supported Rh single site catalysts until the year 2013. In the past 5 years Rh single atoms anchored to different supports were mainly reported for the activation of different small molecules such as CH₄, CO₂, CO, O₂ and NO. For example, the group of Bokhoven characterized an ADMSC of Rh on Al₂O₃ which he used for methane steam reforming.^[71b] CH₄ activation to produce MeOH and CH₃COOH using O₂ and CO under mild conditions was performed by Shan, Li and co-workers using a SAC of Rh supported on TiO₂ or Zeolites.^[71c] Interestingly, Lee, Yi and co-workers were able to tailor the selectivity of CH₄ activation towards MeOH or ethane by performing reactions in the gas phase or in the aqueous phase respectively and using a SAC catalyst of Rh on ZrO₂.^[71d] Other transformations

like CO₂ reduction and CO oxidation have also been reported in the literature. For instance, Christopher and his group synthesized an ADMSC of Rh on TiO₂ for CO₂ reduction to CO and CH₄ using H₂ gas.^[71e] Only Rh single atoms were found to be responsible for the reduction of CO₂ to CO, whereas the larger ensembles were responsible for the formation of methane. The group of Nair used *ab initio* molecular dynamics techniques for investigating CO oxidation and O₂ activation using Rh₁ supported on γ -Al₂O₃ and reported catalytic activity of experimentally intercepted Rh^I(CO)₂ on γ -Al₂O₃.^[71f] CO oxidation was also achieved by the group of Yan by using a SAC of Rh supported on phosphotungstic acid (PTA).^[71g] Interestingly, in 2015 a SSHC type catalyst bearing bimetallic RhCo₃ single sites supported on CoO was shown to be active for the transformation of NO to N₂ using CO.^[71h] Reports on the activity of supported Rh single sites are not limited to small molecule activation. In fact, examples of applications in other chemical transformations like nitro reduction, hydrosilylation and hydroformylation can be found. Lin, Lei and co-workers prepared an SIHC type catalyst with Rh single sites encapsulated within dendritic mesoporous nano channels for the reduction of Nitro phenol.^[71i] The activity of the catalyst was experimentally compared to homogeneous Rh(acac)(CO)₂ and the results were comparable. In addition to this reaction, the catalyst was applied successfully in the hydrosilylation of terminal alkynes to produce α -vinyl silanes. Finally yet importantly, two examples of hydroformylations using Rh single sites were reported recently. When Zhang and his group prepared an SAC catalyst of Rh single atoms on CoO as support, 94% selectivity and an observed TOF of 2065 h⁻¹ were obtained in the hydroformylation of propene.^[71j] Impressively, in the same year Quiao, Zhang and co-workers prepared another SAC consisting of Rh single atoms dispersed on ZnO which was similar in efficiency to the Wilkinson's catalyst ((PPh₃)₃RhCl) and resulted in higher selectivities in the hydroformylation of styrene.^[71k] Several terminal olefins were hydroformylated in toluene, at 100°C during 12 hours reactions using both catalysts. In both cases, TON numbers were up to 40000 depending on the substrate tested. Thus, it is clear from the foregoing that preparation and application of SACs is quite feasible. With this concept, it seems possible to achieve a merger of the best properties of homogeneous catalysis and heterogeneous catalysis in the same catalyst. In addition, it can enable new possibilities such as improved reactivity, selectivity, and yields. Due to the novelty of the technique, the chemistry of Rh SAC and its possible applications remained highly unexplored (section 1.2).

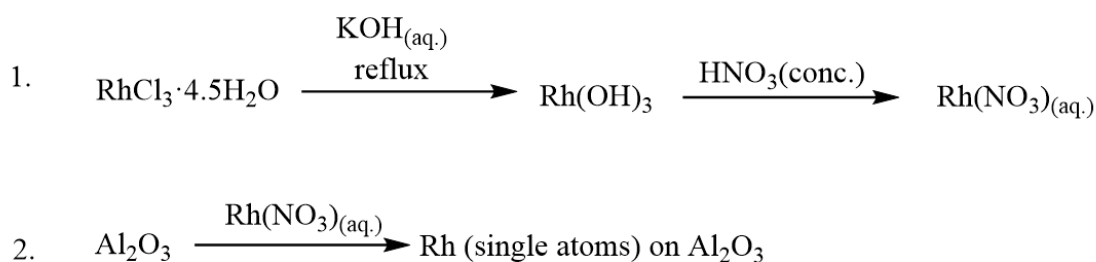
3.2. Objectives

- The goal of
- the work described in this chapter was to explore the selectivity of a Rh SAC on Al₂O₃ in the hydrogenation of a range of different substrates including α,β -unsaturated carbonyl compounds; more interesting is the selective mono-reduction of compounds containing multiple alkenes. In order to assess the special properties of the Rh SAC, the results need to be compared with results obtained using a classical bulk Rhodium on Al₂O₃ catalyst.

3.3. Results and discussion

3.3.1. Synthesis and characterization^[73]

Rh single atoms were introduced to γ -Al₂O₃ by Dr. Wohlrab's group. The synthetic procedure is depicted in Scheme 1. The steps can be summarized as follows: 1. Wet impregnation on γ -Al₂O₃ with a freshly prepared Rh(NO₃)₃ solution which was made by reacting RhCl₃·4.5H₂O and KOH_(aq.) at reflux temperature followed by HNO₃ treatment. Once the wet impregnation is done, it is necessary to remove the excess of water by a very mild evaporation using longer times to avoid metal centres sintering. Otherwise, typically used higher temperatures and low vacuums for drying Rh dispersions will make boiling water create newer defects on the γ -Al₂O₃ structure favouring the formation of Rh aggregates. The last step represents the key for maintaining Rh atoms isolated from each other. Once the material is completely dry, the calcination process is possible with lower risk of aggregation of the Rh atoms. After that, some experiments were performed to characterize it. A complete characterization can be found in 2 recent works.^[73] For us 2 features were especially relevant. Proving the presence of Rh single atoms and determining the exact amount of Rh in the catalyst. Recording X-ray diffraction patterns only the expected reflections of the γ -Al₂O₃ were observed.^[74] The Rh content of the differently loaded catalysts was determined by Inductively coupled plasma(ICP). Results are shown in table 1.



Scheme 1. Schematic synthesis for the Single Atom catalyst of Rh on Al₂O₃.

Table 9. Rh content measurements of different Rh SAC's determined by ICP.

Entry	Catalyst	E.A. result (w.t. %)
1	Rh SAC X	0.554
2	Rh SAC Y	0.722
3	Rh SAC Z	0.071

The HAADF-STEM image of fresh catalyst can be seen in Figure 2. There, brighter Rh single atoms are clearly distinguishable from the γ -Al₂O₃ support. To a lesser extent other small 2 and 3 Rh atom clusters are also observed. Their presence can be tailored by using different Rh(NO₃)₃ concentration in the wet impregnation step (Scheme 1).

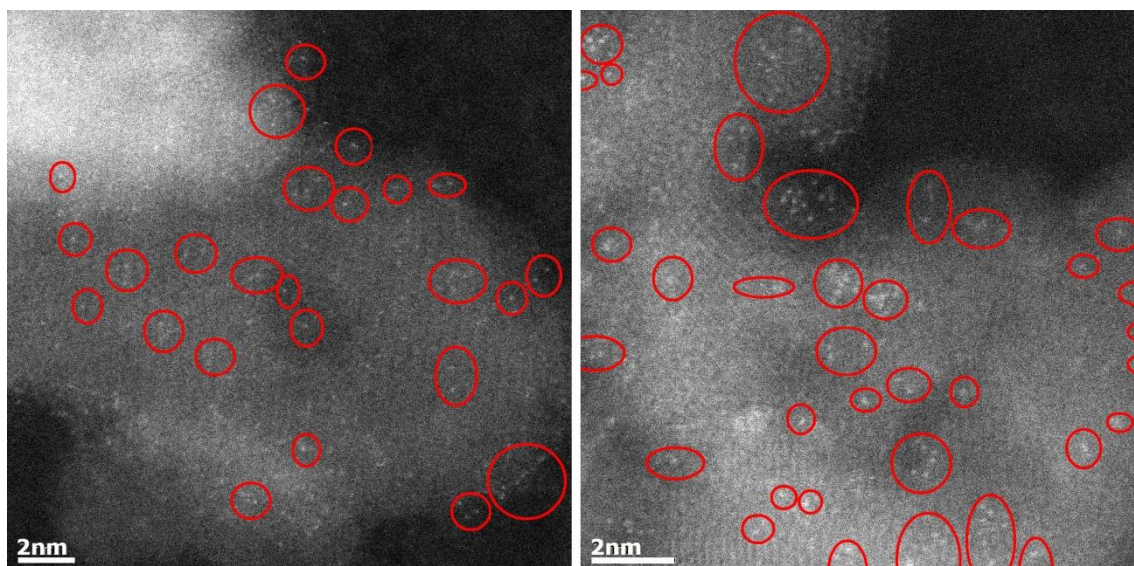


Figure 2. Different HAADF images of fresh Rh single atoms on Al_2O_3 . The Rh content was 1.0mol%. Brighter spots correspond to Rh single atoms, some of them are marked with red circles.

3.3.2. Optimization conditions

Catalyst activation

In the XPS measurements (X-ray photoelectron spectroscopy), the bonding energy observed for the rhodium corresponds to Rh in oxidised states. Thus, with the aim of performing reduction reactions, reducing $\text{Rh}^{\text{X}+}$ to $\text{Rh}^{(0)}$ is needed. In addition, the water content was found to be high due to its hygroscopic character. By gravimetric experiments, the water amount was determined to be as high as 8% of the weight of the catalyst (Figure 3, red line). This water is mainly adsorbed on the surface of the alumina and to a lesser extent on the RhO_x . Removal of this water is a clear requirement to avoid steric hindrance caused by the H_2O molecules in the surroundings of the metal centres and leaving the RhO_x molecules free for being reduced for using in catalysis. Wohlrab and co-workers reported different Temperature program reduction (TPR) experiments on the fresh samples of self-synthesized $\text{Rh}/\text{Al}_2\text{O}_3$.^[73a] In those experiments the end of the reduction peaks under H_2 was observed after 180°C approx.

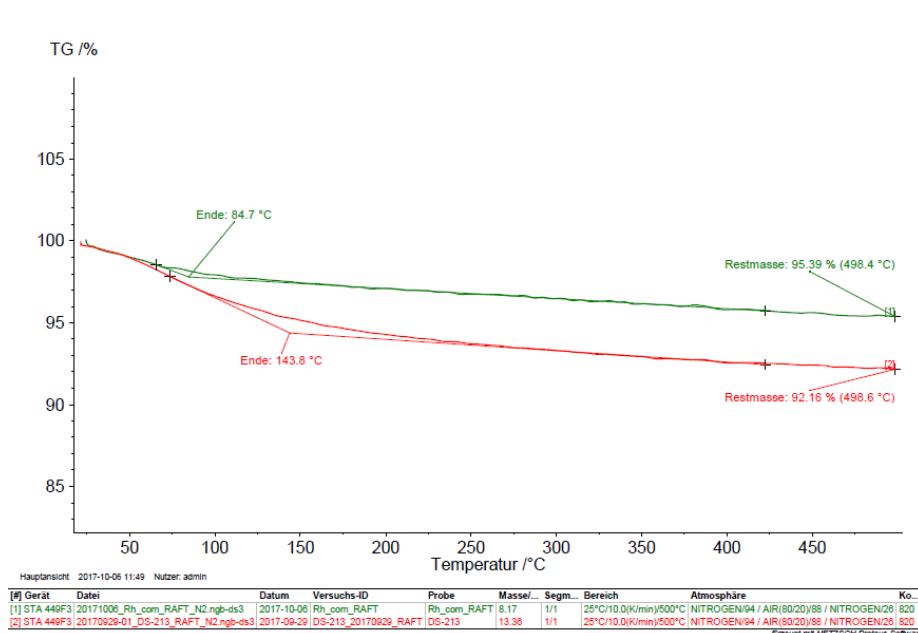
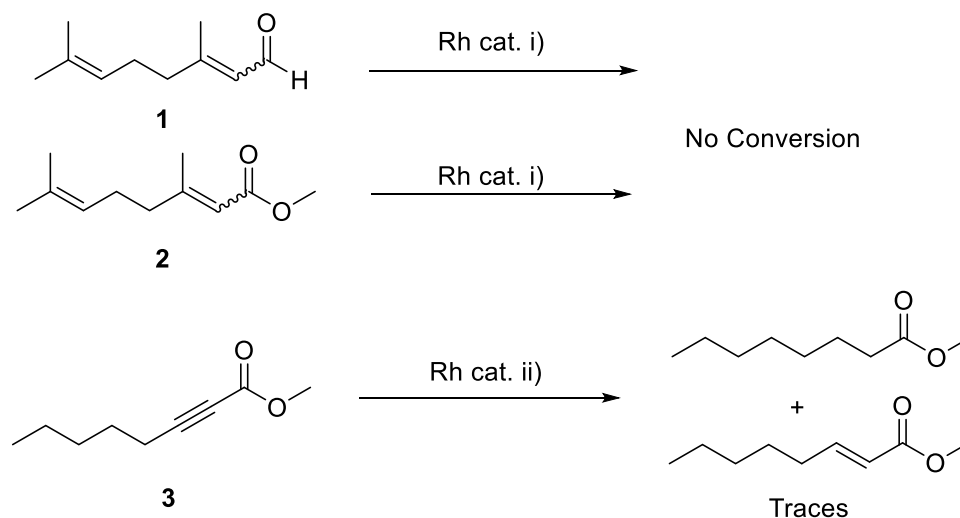


Figure 3. Thermogravimetry for Rh SAC's on Al₂O₃ (Red line) and commercial Rh clusters on Al₂O₃ (Green line).

Therefore we decided to design a pre-treatment protocol prior to catalyst use in order to guarantee the reduction of all the RhOx particles to Rh⁽⁰⁾ and simultaneously to remove the water to obtain a highly active catalyst. This protocol consisted of submitting the catalyst to 200°C and 30 H₂ bars overnight and exchanging carefully the gas phase with fresh H₂ several times during the catalyst activation without cooling it down. This leads to an extremely sensitive catalyst, which needs to be treated under inert conditions to avoid its deactivation, which is mainly caused by air and moisture. From here onwards, the activation step will be not mentioned anymore since it will be always performed without exception in the same fashion.

Preliminary experiments

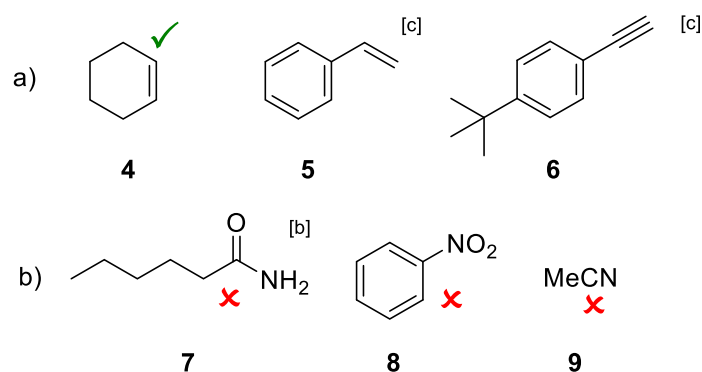
It has already been reported that isolated single atoms can increase the selectivity of different reactions compared to their aggregated counterparts.^[68a-c] For that reason, we wanted to use this Rh SAC X for selective hydrogenation reactions, targeting α,β -unsaturated carbonyl compounds as challenging substrates like we did in the previous chapters. For this, 3 different representative unsaturated carbonyl compounds were selected as substrates for selective hydrogenation. After catalyst activation and without exposing the catalyst to air, the unsaturated substrates were directly added to the activated catalyst under Ar atmosphere inside 45 ml autoclaves. The autoclave was closed, charged with H₂ pressure and stirred vigorously at the indicated temperatures overnight. Unfortunately, GC and GC-MS analysis of the crudes revealed a lack of conversion in all cases (Scheme 2). The reason for this is unclear. However, when methyl 2-octynoate (**3**) was used as substrate some traces of the partially and fully saturated esters were detected in the GC-MS spectrum.



Scheme 2. Conditions i) substrate 12.3 mmol, Rh loading 0.1108 mol% , H_2 (p) = 30 bars H_2 , neat conditions, rt, overnight Conditions ii) Substrate 5.0 mmol, Rh loading 0.022 mol% , H_2 (p) = 25 bars H_2 , neat conditions, 80 °C, overnight.

Scope screening^[a]

These results forced us to reconsider the choice of substrate. Thus, several compounds were screened in the Rh SAC X catalysed hydrogenation. The screening included some unsaturated hydrocarbons (aliphatic and aromatic) as well as some nitrogen containing compounds (Scheme 3). Gratifyingly, when cyclohexene (**4**) was used as substrate full conversion to cyclohexane was observed. On the other hand, when styrene (**5**) and a styrene derivative (**6**) were used as substrates, only traces of saturated compounds were detected and a viscous gel was obtained when the autoclaves were opened after 24 hours reaction. This result can be explained by the acidic nature of the γ - Al_2O_3 and the residual acid from the catalyst synthesis which at this temperature can easily catalyse polymerization of this type of substrate ^[75]. In order not to affect the catalysis the stabilizers in the substrates were removed before the hydrogenation. On the other hand, when nitrogen containing compounds **7-9** (Scheme 3) were tested as substrates no conversion was observed. In the light of these results, we decided to continue our study on the reactivity of Rh SAC X with the hydrogenation of C=C double bonds and to compare these results to those obtained with commercially available Rh clusters supported on Al_2O_3 .

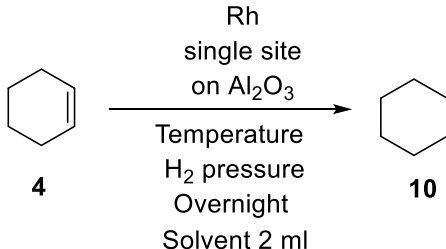


Scheme 1. a) Unsaturated hydrocarbons tested as hydrogenation substrates using Rh SAC X/Al₂O₃ aGeneral conditions: Substrate 1.0 mmol, catalyst loading 0.022 mol%, neat conditions, 80 °C, H₂(p) = 25bars, overnight. bAt the end of the reaction a dense gel was obtained. Presumably polymerization occurred.

Solvent screening

With the future goal in mind of reducing catalyst loadings, times and temperatures, different solvents were tested to check the stability of the activated catalyst in contact with solvents in the hydrogenation of cyclohexene. At first blanks were run. The reaction without catalyst in toluene did not show any conversion (Table 2, entry 1). In the same way when only γ - Al₂O₃ in toluene without Rh was added, no conversion was observed (Table 2, entry 2). As expected when cyclohexene was treated with Rh SAC X (1.1108 mol%) at 150°C with 30 bars of H₂ for 24 hours full conversion to cyclohexene was observed (Table 3, entry 3). More interestingly, in addition to the desired cyclohexane a large amount of methyl cyclohexane was observed which results from the hydrogenation of toluene. Is reported that for Pt catalysed arene hydrogenation catalyst ensembles of at least 3 nm NP's size are required.^[76] Thus, clusters have to be present to cause this type of reactivity. Possibly nanoparticles were formed during the catalyst activation or during the reaction by migration of metal atoms on the surface. Reports on atom migrations leading to larger-sized clusters has been observed with Rh atoms on zeolite^[77] as in other metals on different supports as well^[78] including also single atom catalysts.^[79] Furthermore, it was recently shown that while Rh clusters on Al₂O₃ get reduced to Rh(0) in random spots homogeneously under reduction conditions, the Rh clusters tend to form bigger aggregates of RhO_x under oxidation conditions.^[80] In order to avoid this, the temperature of the reaction was lowered to 100°C and the catalyst loading was lowered to 0.053mol%. With these conditions, no methyl cyclohexane as by-product was observed but also in the same time as previous experiments no full conversion of the starting material was reached (Table 3, entry 4). Apolar solvents like heptane or Et₂O showed only some conversion in the same time (Table 3, entries 5-6). Neither the use of chlorinated solvents nor the use of alcoholic solvents led to full conversion after 24 hours reaction (Table 2, entries 7-11). However, performing the reaction under neat conditions led to full conversion of cyclohexene to cyclohexane (Table 2, entry 12) as was already demonstrated in the previous experiments.

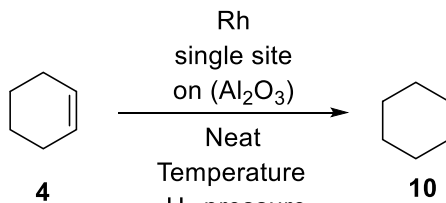
Table 10. Solvent screening for the Hydrogenation of cyclohexene with single-site Rh on Al₂O₃ catalyst^a

<div style="text-align: center;">  </div>					
Entry	Solvent	Full Conversion	Entry	Solvent	Full Conversion
1	Toluene	✗ ^{b,c}	7	CHCl ₃	✗
2	Toluene	✗ ^{b,d}	8	CH ₂ Cl ₂	✗
3	Toluene	✓ ^{b,e}	9	MeOH	✗
4	Toluene	✗	10	EtOH	✗
5	Heptane	✗	11	THF	✗ ^f
6	Et ₂ O	✗	12	Neat	✓

^aReaction conditions: Substrate (1.0 mmol), Catalyst loading 0.053 mol%, Solvent (2.0 mL), H₂ (p) = 25 bars, 100°C, overnight. ^bReaction conditions: Substrate (1.0 mmol), Catalyst loading 1.11 mol%, Solvent (2 mL), H₂ (p) = 30 bars, 150°C, overnight. ^cNo catalyst was used. ^dAl₂O₃ without Rh was used. ^eMethyl cyclohexane was detected as by-product. ^fReaction Conditions: Substrate (1.0 mmol), Catalyst loading: 0.1108 mol%, Solvent (2 mL), H₂ (p) = 30 bars, 150 °C, overnight.

As was seen in the preliminary experiments, the presence of heteroatoms in the media seems to result in catalyst poisoning of the Rh single atom catalyst. Using neat conditions reduces the possible poisoning of the catalyst by the residual ppms of water coming from the solvents. Next, temperature, time and pressure were optimized. Results are summarized in table 3. Impressively, it was possible to reduce the temperature down to ambient with no loss of conversion (Table 3, entry 2). The same happened when time was reduced; it was possible to obtain the same conversion within only 5 minutes at room temperature (Table 2, entry 3). Interestingly, supplying the hydrogen via a balloon was sufficient for obtaining full conversion of cyclohexene at room temperature, although at the expense of reaction time. It was necessary to run the reaction overnight (Table 3, entries 5, 7). With only 20 minutes reaction time a 37% GC yield was obtained (Table 3, entry 7). For comparison a similar catalyst was purchased, bulk Rh on Al₂O₃ (0.5 wt%). Contrary to what was seen with Rh SAC X, XPS of commercial catalyst showed bonding energies corresponding to Rh-Rh bonds, this corroborates the presence of Rh clusters. This catalyst was submitted to the same activation protocol followed for the Rh SAC X and used for the same hydrogenation reactions under the same conditions. We expected to see faster reaction in the cyclohexene hydrogenation when Rh SAC X was used because single atoms are reported to be more active H₂ dissociation^[83a] and because of the fact of having much more Rh active centres in comparison to commercial one. However, against our expectations, the results obtained with both Rh SA X and commercially available Rh on Al₂O₃ catalysts were almost identical (Table 3, entries 6, 8) if not slightly lower in the case of

Table 11. Optimization for the conditions of the hydrogenation of cyclohexene with single-site Rh on Al₂O₃ catalyst and Rh on Al₂O₃ commercial catalyst.^a



Entry	Rh source	Temp.	Time	Pressure	Conv. [%]	Yield [%]
1	Single atom	150	overnight	30	>99	>99%
2	Single atom	rt	overnight	30	>99	>99
3	Single atom	rt	5	30	>99	>99
4	Single atom	rt	5	4	>99	>99
5	Single atom	rt	overnight	H ₂ balloon	>99	>99
6	Commercial	rt	overnight	H ₂ balloon	>99	>99
7	Single atom	rt	20	H₂ balloon	37	37
8	Commercial	rt	20	H₂ balloon	39	39

^aGeneral conditions: Substrate (1.0 mmol), Catalyst loading 0.053mol%, Conversions and yields were determined by GC using dodecane as internal standard, Time in minutes otherwise indicated.

Rh SAC X. As happened in the hydrogenation of cyclohexene in Table 2 entry 3, conditions in the pre-treatment catalyst or during reaction may lead to the formation of Rh aggregates which will further behave more similar to commercial bulk Rh catalyst. In order to get more hints for more solid explanation of these differences, monitorings were performed with both catalysts in the hydrogenation of different substrates.

3.3.3. Reactivity comparison

Intrigued by the similar results obtained with both Rh catalysts, it was decided to monitor the reaction in order to obtain a more precise kinetic profile and to study possible deactivation. Towards that goal, a parallel reactor system with automated sampling under reaction conditions (SPR16 SLURRY PHASE REACTOR) was used in order to obtain these data without losing the inert conditions that are required for the Rh SAC X (Figure 4). Due to certain logistics related to the minimum conditions required for the machine, the temperature was fixed at 30°C and the H₂ pressure was increased to 15 bars and kept isobaric. In order to obtain reaction times long enough to allow comparison, the catalyst loading was reduced to 0.01108 mol%. Whereas these conditions lead to full conversion of cyclohexene in 34 minutes using Rh SAC X, the

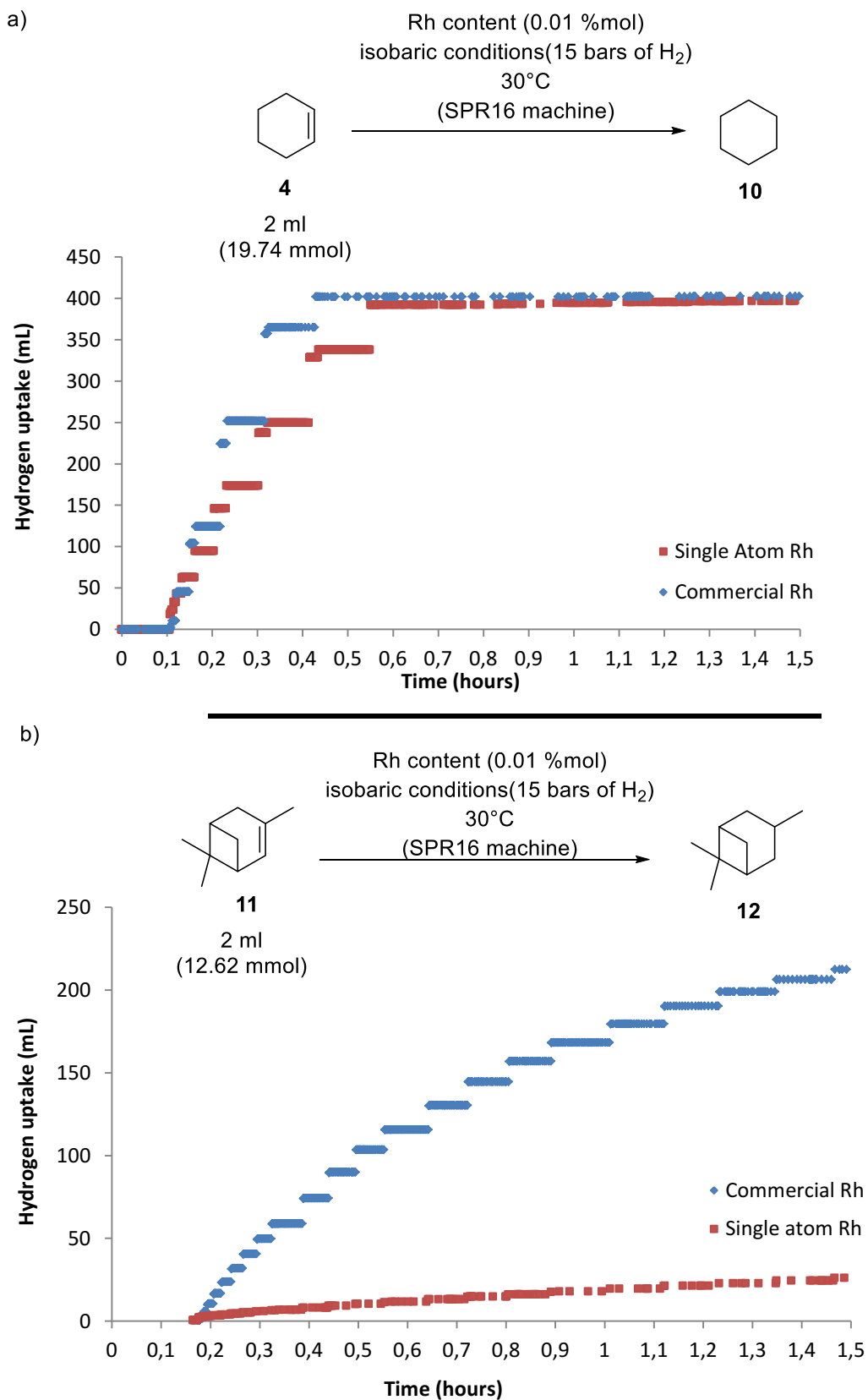


Figure 4. Monitoring of the H₂ uptake using SPR16 machine and isobaric conditions in the hydrogenations of: a) Cyclohexene. b) α -Pinene; using commercial Rh/Al₂O₃ (Blue line) and Rh SAC X (Red line).

commercial Rh catalyst achieved this in 26 minutes. In the light of these results approximated TOFs were also calculated when 50% of the total volume of H₂ was consumed. For Rh SAC X this was 417 s⁻¹ and for the commercial catalyst turned out to be 857 s⁻¹. This large difference in rate depending on the size of the clusters is in accord with Corma's report on the influence of the Pt nano-particles size in the C=C hydrogenation.^[81] He and his group developed a series of different sized Pt nanoparticles on Al₂O₃ for the selective hydrogenation of the NO₂ group of *m*-nitro styrene. They demonstrated that the smaller the Pt particle size, the lower the rate of the C=C double bond hydrogenation of styrene and *m*-NO₂-styrene. Recently, based on these observations, Wei developed FeO_x supported Pt single atom catalyst for the same purpose.^[82] In this work by lowering the size of the Fe nanoparticles to single atoms and very small clusters was possible to inhibit the activity on the C=C double bond hydrogenation in order to reduce selectively the nitro group on *m*-NO₂-styrene. This leads to conclusion that clusters are needed for activity in C=C hydrogenation and the opposite has to be true as well, the smaller the cluster the lower the activity for C=C hydrogenation. This correlation between the metal cluster size and the activity for C=C hydrogenation was also reported by other groups.^[83] It is clear that whereas the commercial Rh/Al₂O₃ catalyst that we have used has larger particles, the Rh SAC X consists mostly of single rhodium atoms and a small amount of small clusters. Therefore, if atoms on corners of the crystallites of Rh clusters are needed as well as in Pt cases for better hydrogenation of C=C double bonds, would be the case that Rh single atoms which do not bear "corners" will give lower hydrogenation rates in the hydrogenation of C=C unsaturations.

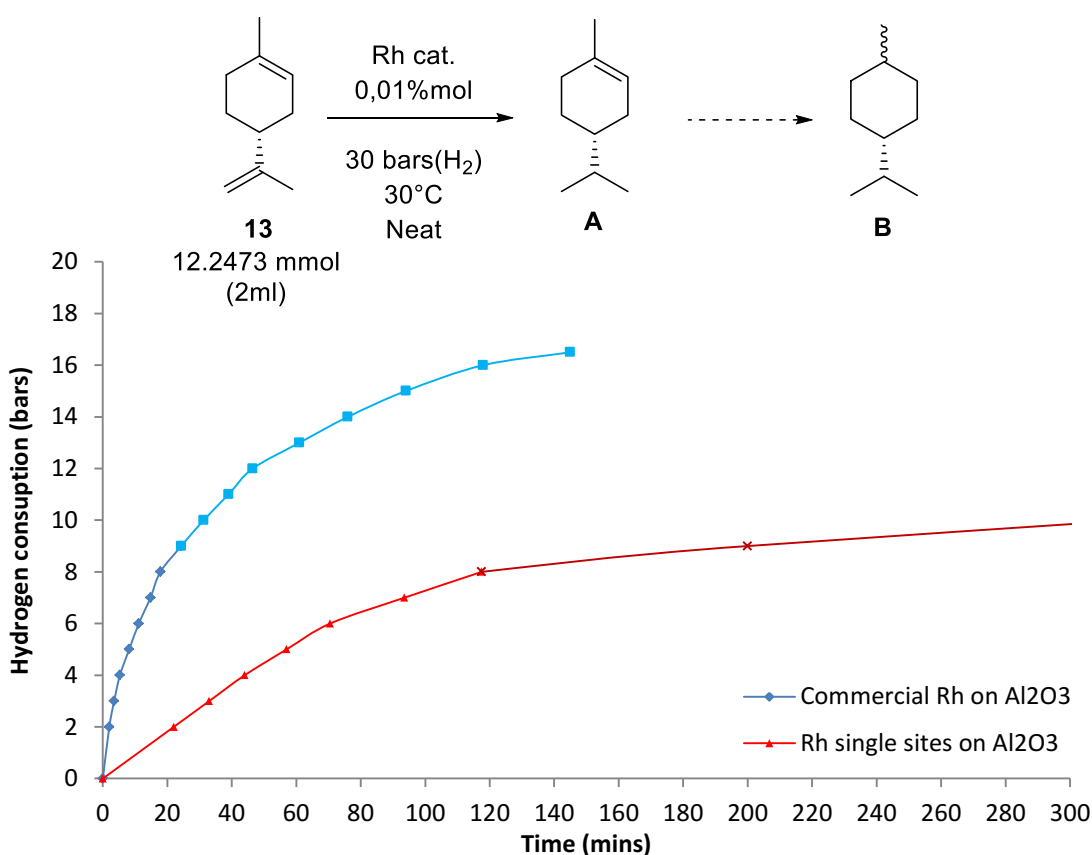
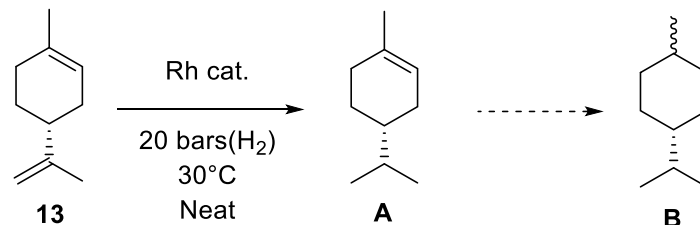


Figure 5. Monitoring for the hydrogen uptake in the hydrogenation of Limonene using commercial Rh/Al₂O₃ (Blue line) and Rh SAC X (Red line). Hydrogen was measured directly from the value of the barometer installed in the autoclave.

Indeed, this fits with our experimental results. This effect was even more pronounced when a more sterically hindered olefin like α -Pinene was used as substrate (Figure 4). In this case, the commercial rhodium catalyst showed an approximate TOF of 197 s^{-1} when 50% of the total volume of H_2 was consumed. Therefore the α -Pinene hydrogenation rate is lower than that of cyclohexene. Indeed 1,5 h were needed for complete conversion compared to the 0,45 h needed for cyclohexene hydrogenation. Thus, substituents on the double bond lead to a reduction in rate of the hydrogenation. For the Rh SAC X counterpart the steric hindrance effect was much more pronounced, to the point that for the hydrogenation of α -Pinene in the same time period only 12% of the hydrogen needed for complete conversion was consumed. This corroborates again the correlation between particle size and activity for unpolarized $\text{C}=\text{C}$ double bonds. In the light of these results we thought it would be interesting to explore the possibility that the Rh SAC X can be used for the selective reduction of the least hindered double bond in substrates with multiple unsaturations. A good target compound would be Limonene which has one terminal vinylidene and one tri-substituted double bond. Limonene is a monoterpene formed by 2 isoprene units. This compound can be obtained by steam distillation of citrus peels. Limonene is used as fragrance or flavorant in cosmetics, and in the fragrance and food industries. But it is also used in fine chemicals, insect control for agriculture and in the production of biofuels.^[84] When Limonene is selectively hydrogenated, 1-menthene can be obtained. 1-menthene has been used as a precursor for drug synthesis and as additive in the formulation of coatings and adhesives.^[85] To study the potential of Rh SAC X for selective limonene hydrogenation in comparison with commercial $\text{Rh}/\text{Al}_2\text{O}_3$, the reactions were monitored recording the hydrogen uptake (Figure 6). Limonene hydrogenations were initially performed using 0.01mol% Rh of both catalysts at 30°C . Using the ideal gas law as a fair approximation it was calculated that with the amount of substrate used, each $\text{C}=\text{C}$ double bond will consume 7.1 bars of H_2 . For that reason, 30 bar of hydrogen were charged. As can be seen in Figure 5 (blue line), after 145 minutes reaction, 16.5 bars of H_2 were consumed using the commercial rhodium catalyst. GC-MS spectra showed p-menthane as the main product. On the other hand, Rh SAC X on Al_2O_3 consumed 8.2 bars H_2 during the same time. Furthermore, the rate of H_2 consumption after that point decreased tremendously. Then, runs with different catalyst loadings were performed in order to record the selectivities in both cases; the results are summarized in Table 4. When limonene was stirred under neat conditions in the presence of commercial Rh on Al_2O_3 (0.01 mol%) only 30 minutes were necessary to get full conversion

Table 12. Comparison of the selectivity of Rh catalysts in the hydrogenation of Limonene.^a

							
Entry	Catalyst	Loading [mol%]	Time [minutes]	Conv. [%] ^c	Yield A [%] ^c	Selectivity towards A [%] ^c	Yield B [%] ^c
1 ^b	Rh/ Al_2O_3	0.01	30	>99	68	68	---
2	Rh SAC X	0.01108	30	72	60	83	---

3	Rh SAC Y	0.077	7.5	>99	79	79	---
4	Rh SAC Z	0.071	15	>99	98	98	---
5^b	Rh/Al ₂ O ₃	0.0028	3,5 ^d	>99 ^e	87 ^e	88	6 ^e
6	Rh SAC X	0.0028	26 ^d	91 ^e	85 ^e	93	7 ^e

^aReaction conditions: autoclave (V = 45 mL) Substrate 12.3 mmol, neat conditions, 20 bars of H₂ gas only to guarantee enough mmols of hydrogen for complete conversion of the substrate. ^b Commercially available catalyst. ^cDetermined by ¹H-NMR using hexamethyl siloxane as internal standard ^dTime in hours. ^eDetermined by GC using hexamethyl siloxane as internal standard.

of the starting material (Table 4, entry 1). However, selectivity was 68% and the rest was identified as the fully hydrogenated product. Running the same experiment with Rh SAC X led to 72% conversion after 30 minutes and 60% yield of 1-menthene and 83% selectivity (Table 4, entry 2). Therefore, selectivity was clearly higher for the Rh SAC X. When the catalyst loading was reduced 4 times the selectivity of the hydrogenation of limonene was increased to 88% using Commercial Rh/Al₂O₃ (Table 4, entry 5). However the time needed to achieve full conversion was also increased to 3.5 hours. In the case of the Rh SAC X catalyst selectivity also increased to 93% (Table 4, entry 6) Nevertheless, this improvement was at the expense of a large decrease of the reaction rate, indeed, after 26 hours the conversion was 91%. Therefore, at this catalyst loading, the selectivity was still higher when Rh SAC X was used. However rates that allow conversion within a few hours are highly desired. In order to maintain the Rh loading but to prevent cluster formation during the activation protocol new batches of catalyst were synthesized containing even lower amounts of Rh (Section 2.1 Table 1). As expected, when the Rh content of the catalyst was increased to 0.722 wt% (Table 1, entry 2, SAC Y) the selectivity in the hydrogenation of limonene slightly decreased to 79% (Table 4, entry 3). Gratifyingly, catalyst Rh SAC Z which contains only 0.071wt% of Rh (Table 1, entry 3) allowed full conversion and selectivity in only 15 minutes using 0,071mol% of Rh (Table 4, entry 3). After these experiments, we performed a comparison of our best results of both Rh catalysts with the reported results of commercially available catalysts based on other metals and a Rh(0) catalyst with a different support material in the selective hydrogenation of Limonene (Table 5). In addition to the suitability of Al₂O₃ as support for rhodium in the selective hydrogenation of Limonene as reported by Leitner,^[85] also the use of Montmorillonite as support was shown to lead to very high selectivities.^[86] In summary, the table shows that rates and selectivities were much higher when commercial Rh on Al₂O₃ was used as catalyst compared to all other commercial catalysts studied by Leitner (Table 1, entries 1-7,10-11,13). In that work the best selectivity reported was obtained using Ru/SiO₂, however 24 hours were required to achieve full conversion. (Table 4, entry 5). The commercial catalyst which presented comparable rates with highest selectivities was Pt/C (Table 4, entry 5). Still the 83% selectivity obtained with Pt/C was lower than the 87% obtained with the commercial Rh/Al₂O₃ (Table 5, entry 11). It is clear that the use of Rh SAC X on Al₂O₃ can improve the selectivity in comparison to the commercial Rh/Al₂O₃ (Table 4, entry 13). Interestingly, Ganguli synthesized a catalyst bearing Rh (0) NPs supported on montmorillonite k-10 clay.^[86] This catalyst showed 99% selectivity when limonene was used as substrate in MeOH as solvent suggesting montmorillonite k-10 clay as a very good support for selective limonene hydrogenation (Table 5, entry12). Recently, a

heterogeneous iridium catalyst supported on a custom made Nano sponge of BNH_x also gave high selectivities taking 4,5 hours and 0,1 mol% catalyst loading. (Table 4, entry 14).

Table 13. Comparison of the performance of different commercial available catalysts and custom ones for the selective hydrogenation of Limonene.

13 **A**

Entry	Catalyst ^a	Cat.Load [mol%]	H ₂ (p) [bars]	Time [hours]	Conv. [%] ^c	Select. [%] ^c	Ref.
1 ^b	Pd/C	0.025	3	5	89	45	[85]
2 ^b	Ru/C	0.025	3	-	-	-	[85]
3 ^b	Ru/Al ₂ O ₃	0.025	3	-	-	-	[85]
4 ^b	Ru/SiO ₂	0.025	3	24	>99	95	[85]
5 ^b	Pt/C	0.025	3	2	>99	83	[85]
6 ^b	Pt/Al ₂ O ₃	0.025	3	5	>99	78	[85]
7 ^b	Pt/SiO ₂	0.025	3	>10	>99	43	[85]
8	Pt-Zeolite4A(A)	3.7	1	1,5	---	59 ^h	[87]
9	(Pt)5cCVDA	3.7	1	1	---	88 ^h	[87]
10 ^c	Rh/Al ₂ O ₃	0.02	20	0,3	>99 ^f	77 ^f	This work
11 ^c	Rh/Al ₂ O ₃	0.0028	20	3,5	>99	87 ^f	This work
12 ^d	Rh/ Montmorillonite	0.5	2,5	0,71	>99 ^g	>99 ^g	[86]
13 ^c	Rh SAC Z/Al ₂ O ₃	0.071	20	0,25	>99 ^f	98 ^f	This work
14	Ir/BNH _x (Nano sponge)	0.1	4	4,5	>99	<98	[88]

^aAll catalysts are commercially available with the exception of entries 12-14. ^bReaction conditions: batch reactor (V = 20 mL), Substrate 6 mmol, neat conditions. ^cReaction conditions: autoclave (V = 45 mL) Substrate 12.24 mmol, neat conditions, 20 bars of H₂. ^d Reaction conditions: Substrate 1 mmol, MeOH (15 mL). ^eDetermined by GC using n-dodecane as internal standard. ^fDetermined by ¹H-NMR using hexamethyl siloxane as internal standard. ^gDetermined by GCMS. ^hValue corresponds to yield. Conversions are not given.

3.4. Conclusions and Further prospects

Conclusions

- The use of Rh SAC supported on Al₂O₃ was explored for the hydrogenation of α,β unsaturated carbonyl compounds. However, no activity was observed.
- Carbon-carbon double bond hydrogenation was explored using Rh SAC supported on Al₂O₃ and commercial bulk Rh/Al₂O₃ for comparison. Whereas the use of Rh SAC and bulk Rh/Al₂O₃ led to very similar results in the hydrogenation of cyclohexene, the single atom rhodium catalyst was much slower in the hydrogenation of higher substituted olefins such as Pinene. This allowed the selective reduction of the less

substituted double bond in substrates containing multiple unsaturations, such as Limonene with the rhodium single atom catalysts. Reduction with bulk Rh/ Al₂O₃ was less selective.

- The selectivities of the hydrogenation of Limonene were compared to those reported in the literature, showing the high potential of decreasing the Rh loading on the support forming more isolated Rh atoms to increase selectivities towards different olefins.

Further Prospects

- In order to increase the Rh loadings on the support while maintaining the selectivity better activation protocols need to be designed to avoid atom migrations and cluster formation.
- The scope and the limitations of the system for differently substituted olefins need to be explored using compounds like non-oxidized terpenes.
- Also, selective hydrogenation of the carbon-carbon triple bond needs to be explored. Finally, a comparison with other homogeneous Rh catalysts like the Wilkinson catalyst and Rh(acac)(CO)₂ could give a better understanding of the possible improvements achieved by Rh SAC on Al₂O₃.

4. Summary

Selective Hydrogenation and Transfer-Hydrogenation reactions

This dissertation describes the research on catalysts active for the selective transfer hydrogenation (TH) of α,β -unsaturated carbonyl compounds using EtOH as H_2 source as alternative to commonly used iPrOH. A handy protocol for reducing α,β -unsaturated ketone and aldehyde compounds using commercial available homogeneous ruthenium catalyst is described and applied in the reduction of interesting renewable substrates. Furthermore, a base-free iron based protocol is designed and optimized for the novel TH of ester compounds using EtOH as H_2 source. With this protocol, very relevant substrates in renewable chemistry are smoothly reduced. The scope includes substrates like adipic acid dimethyl ester and even a polyester compound. In addition, the chemical activity of new single rhodium atoms on Al_2O_3 is explored. Using limonene as a model compound, only the terminal olefin was hydrogenated and the potential selective character of the catalyst is highlighted.

Selektive Hydrierungen und Transfer-Hydrierungen

Diese Dissertation beschreibt Untersuchungen an Katalysatoren zur selektiven Transferhydrierung (TH) von α,β -ungesättigten Carbonylverbindungen. Insbesondere wird die Anwendbarkeit von Ethanol als alternative Wasserstoffquelle zu dem weitverbreiteten iPrOH beschrieben und diskutiert. Weiterhin wird ein effizientes Protokoll für die Reduktion von α,β -ungesättigten Ketonen und Aldehyden mit einem kommerziell verfügbaren homogenen Ruthenium-Katalysator beschrieben und auf bio-basierte Substrate angewendet. Weiterhin wurde auf einen Homogenen Eisen-Katalysator beruhendes Basen-freies Protokoll für die bis dahin unbekannte TH von Carbonsäureestern entwickelt, das ebenfalls Ethanol als Wasserstoffquelle einsetzt. Mit diesem Protokoll können relevante Substrate aus erneuerbaren Ressourcen reduziert werden. Darüberhinaus war es möglich auch einen Polyester zu den korrespondierenden Diolen zu depolymerisieren. Zusätzlich beschreibt die vorliegende Arbeit, die katalytische Aktivität von Rhodium-Single-Atom Katalysatoren, in der Reduktion von Olefinen. Es war möglich bei der Modellverbindung Limonen nur die terminale Olefinbindung zu hydrogenieren, was den Selektiven Charakter des Katalysators unterstreicht.

5. Experimental part

5.1. General considerations

All substrates were purchased from T.C.I., Sigma Aldrich or abcr GmbH. To remove peroxides, substrates were distilled over $P(Ph)_3$ prior to use when difference in boiling point allowed it. The complex Ru-MACHOTM-BH was purchased from Strem Chemicals and used without any further purification. Ruthenacycle (**4**),^[34] Rh complex (**3**),^[33c] and compound (**9rb**)^[89] Fe-MACHO-BH (**3**)^[54a] and Mn-MACHO-BH (**6**)^[55] were synthesized according to the literature procedures. EtOH was obtained from a solvent purification system. Dry iPrOH was purchased from Across Organics, degassed and purged with argon prior use. Aluminium TLC plates coated with silica gel 60 F₂₅₄ were purchased from Merck. $KMnO_4$ stain was used for developing TLC plates. The stain solution was prepared by dissolving 3 g of $KMnO_4$ and 20 g of K_2CO_3 in 300 ml of H_2O and 5 ml of 5% NaOH aqueous solution. NMR spectra were recorded on Bruker AV 300 MHz and Bruker AV 400 MHz spectrometers. 1H and ^{13}C -NMR spectra were referenced to residual solvent peaks of CD_2Cl_2 (5.32 ppm and 53.84 ppm respectively) or Chloroform-*d* (7.26 ppm 77.16 ppm respectively). All chemical shifts are reported in ppm, coupling constants in Hz. Abbreviations are: s:singlet, d:doublet, t:triplet, q:quadruplet, quin: quintuplet, m:multiplet, br: broad. GC-FID analysis was carried out on an Agilent 7890B GC system with a HP-5 normal-phase silica column, using He as a carrier gas and dodecane as internal standard. GC-MS spectra were recorded with a combination of an Agilent Technologies GC Mass 5973 Network MSD and an Agilent Technology 6890N Network GC System. HR-MS measurements were recorded on an Agilent 6210 time-of-flight LC/MS (ESI) or on a Thermo Electron MAT 95-XP (EI, 70 eV). Peaks as listed correspond to the highest abundant peak and are the expected isotope pattern. Powder X-ray diffraction (XRD) patterns of the calcinated samples were measured in angle range from 5 – 80° 2Theta scale on a Theta/Theta diffractometer X'Pert Pro from analytical, Almelo, Netherlands using Ni-filtered Cu-K $_{\alpha}$ radiation (λ = 1.5418 Å, 40 kV, 40 mA). The data were recorded with the X'Celerator (RTMS) detector. TEM (transmission electron microscopy) measurements at 200 kV were performed on a JEMARM200F (JEOL) with aberration-correction by a CESCOR (CEOS) for the scanning transmission (STEM) applications. A Varian 715-ES ICP-OES (Inductively Coupled Plasma-Optical Emission Spectrometer) was used for the determination of the elemental composition of the catalysts after complete dissolution in a solution containing 8 mL of aqua regia and 2 mL hydrofluoric acid.

5.2. Chapter 1

5.2.1. Experimental procedures

General reaction procedure for the Ru-MACHOTM-BH catalysed transfer hydrogenation

A dry 50 ml Schlenk round-bottom flask provided with a stirring magnet was purged with 3 Argon-Vacuum cycles and charged with a solution of 4.7 mmol substrate in 20mL of solvent. The corresponding catalyst loading was added via syringe as a stock solution in anhydrous CH₂Cl₂ (17mM). The reaction mixture was stirred at alcohol reflux. Reaction advance was monitored with T.L.C. and GC until starting material was fully converted or no more advance was observed (from 2 to 30 minutes depending on the substrate). After that, reaction mixture was filtered over silica and solvents were removed. The resulting product was purified by column chromatography (SiO₂;Cyclohexene:AcOEt, 4:1) with exception of compounds **9h** and **9a** which were distilled using a kugelrohr and an azeotropic distillation respectively.

Monitoring experiments for substrate **8r**

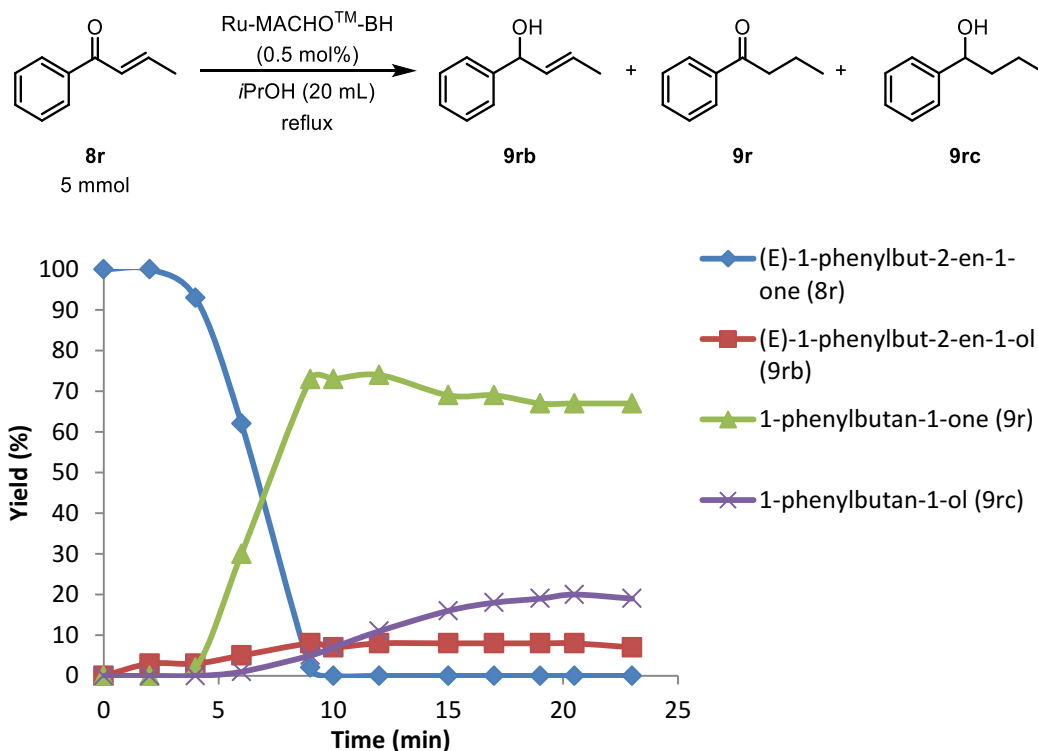


Figure E 1. Reaction monitoring of compound **8r** with GC using dodecane as internal standard.

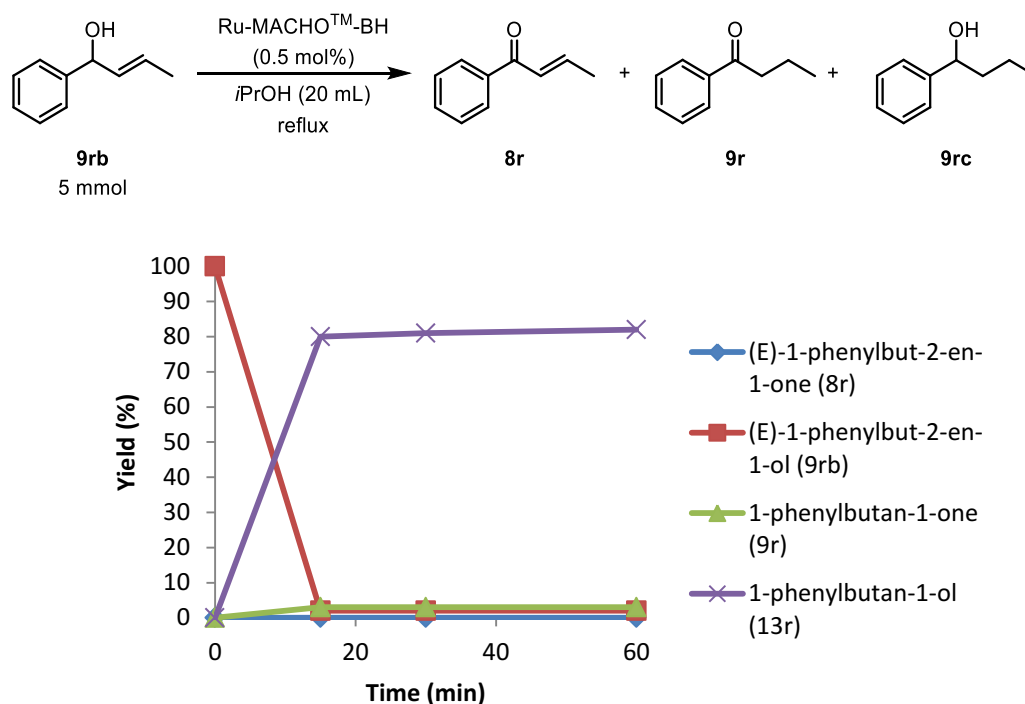


Figure E 2. Reaction monitoring for (E)-1-phenylbut-2-en-1-ol (**9rb**) with GC using dodecane as internal standard.

5.2.2. Analytical data and spectra

Crotyl alcohol (**9a**):

¹H-NMR (300 MHz, Methylene Chloride-*d*₂) δ 5.74 – 5.46 (m, 2H), 3.96 (t, *J* = 4.5 Hz, 2H), 1.65–1.58 (m, 3H), 1.57 – 1.47 (m_{br}, 1H).

¹³C-NMR (75 MHz, Methylene Chloride-*d*₂) δ 130.8 (CH), 127.9 (CH), 63.8 (CH₂), 17.8 (CH₃).

HRMS (EI): *m/z* calc. for C₄H₈O: 72.05697; found: 72.05722 [M]⁺

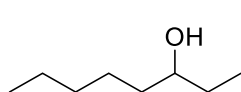
1-Octanol (**9b**):

¹H-NMR (300 MHz, Chloroform-*d*) δ 3.62 (t, *J* = 6.5 Hz, 1H), 1.74 – 1.48 (m_{br}, 3H), 1.40 – 1.20 (m, 10H), 0.97 – 0.73 (m, *J* = 7 Hz, 3H).

¹³C-NMR (75 MHz, Chloroform-*d*) δ 63.1 (CH₂), 32.9 (CH₂), 31.9 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 25.8 (CH₂), 22.7 (CH₂), 14.2 (CH₃).

HRMS (EI): *m/z* calc. for C₈H₁₇O: 129.12739; found: 129.12682 [M]⁺

3-Octanol (9c):

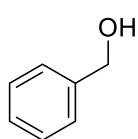


¹H-NMR (300 MHz, Chloroform-*d*) δ 3.52 (m, 1H), 1.63 – 1.19 (m, 12H), 0.93 (t, J = 7.5 Hz, 3H), 0.83 (t, J = 6.5 Hz, 3H).

¹³C-NMR (75 MHz, Chloroform-*d*) δ 73.4 (CH), 37.0 (CH₂), 32.0 (CH₂), 30.2 (CH₂), 25.4 (CH₂), 22.7 (CH₂), 14.1 (CH₃), 10.0 (CH₃).

HRMS (ESI-TOF): m/z calc. for C₈H₁₇ONa: 153.12499; found: 153.12502 [M+Na]⁺

Phenyl methanol (9d):

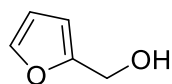


¹H-NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.27 (m, 5H), 4.69 (d, J = 4.5 Hz, 2H), 1.86 (s_{br}, 1H).

¹³C-NMR (75 MHz, Chloroform-*d*) δ 140.55 (C), 128.26 (CH), 127.36 (CH), 126.69 (CH), 65.06 (CH₂).

HRMS (EI): m/z calc. for C₇H₈O: 108.05706; found: 108.05679 [M]⁺

Furan-2-ylmethanol (9e):

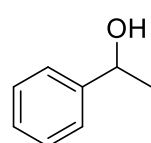


¹H-NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.42 (dd, J = 2.0, 1.0 Hz, 1H), 6.36 (dd, J = 3.0, 2.0 Hz, 1H), 6.29 (dd, J = 3.0, 1.0 Hz, 1H), 4.57 (d, J = 5.5 Hz, 2H), 1.90 (t, J = 6.0 Hz, 1H).

¹³C-NMR (75 MHz, Methylene Chloride-*d*₂) δ 154.8 (CH), 142.8 (CH), 110.7 (CH), 57.6 (CH₂).

HRMS (ESI-TOF/MS) m/z calc. for C₅H₆O₂Na: 121.026 found 121.02618 [M+Na]⁺,

1-Phenylethan-1-ol (9f):

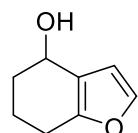


¹H-NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.23 (m, 5H), 4.90 (q, CH, J = 6.5 Hz, 1H), 1.89 (s, 1H), 1.50 (d, CH₃, J = 6.5 Hz, 3H).

¹³C-NMR (75 MHz, Chloroform-*d*) δ 145.9 (C), 128.6 (CH), 127.6 (CH), 125.5 (CH), 70.5 (CH), 25.3 (CH₃).

HRMS (EI) m/z calc. for C₈H₁₀O: 122.07262, found: 122,07249

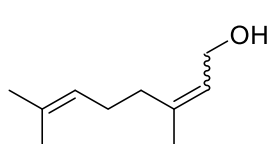
4,5,6,7-Tetrahydrobenzofuran-4-ol (9g):



¹H-NMR (300 MHz, Methylene Chloride-*d*₂) δ 7.30-7.24 (m, 1H), 6.39 (d, J = 2.0 Hz, 1H), 4.69 (m_{br}, 1H), 2.70 – 2.40 (m, 2H), 2.01 – 1.71 (m, 4H), 1.71 (s_{br}, 1H).

^{13}C -NMR (75 MHz, Methylene Chloride- d_2) δ 152.9 (C), 141.2 (C), 120.61 (CH), 109.5 (CH), 64.3 (CH), 33.1 (CH₂), 23.3 (CH₂), 19.4 (CH₂). **HRMS** (ESI-TOF/MS) m/z calc. for C₈H₁₀O₂Na: 161.05723, found 161.05751 [M+Na]⁺

Nerol-Geraniol (mixture) (9h):

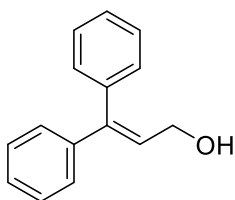


^1H -NMR (300 MHz, Chloroform- d) δ 5.42 (q_{br}, J = 7.0 Hz, 1H), 5.14–5.04 (m_{br}, 1H), 4.20 – 4.01 (m, 2H), 2.13 – 1.99 (m, 4H), 1.76 – 1.65 (m, 6H), 1.60 (s_{br}, 3H), 1.26 (s_{br}, 1H).

^{13}C -NMR (75 MHz, Chloroform- d) δ 140.0 (C), 139.87 (C), 132.5 (C), 131.8 (C), 124.5 (CH), 124.0 (CH), 123.9 (CH), 123.4 (CH), 59.5 (CH₂), 59.1 (CH₂), 39.6 (CH₂), 32.0 (CH₂), 26.6 (CH₂), 26.5 (CH₂), 25.8 (CH₃), 25.7 (CH₃), 23.5 (CH₃), 17.8 (CH₃), 17.7 (CH₃), 16.4 (CH₃).

HRMS (EI): m/z calc. for C₁₀H₁₈O 154.13522, found: 154.13553

β -phenyl cinammylalcohol (9i):

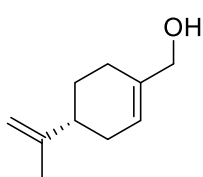


^1H -NMR (400 MHz, Methylene Chloride- d_2) δ 7.46 – 7.11 (m, 10H), 6.23 (t, J = 7.0 Hz, 1H), 4.17 (dd, J = 7.0, 5.5 Hz, 2H), 1.47 (t, J = 5.5 Hz, 1H)

^{13}C -NMR (101 MHz, Methylene Chloride- d_2) δ 144.23 (C), 142.34 (C), 139.57 (C), 130.10 (CH), 128.57 (CH), 128.54 (CH), 128.31 (CH), 127.93 (CH), 127.89 (CH), 60.91 (CH₂).

HRMS (ESI-TOF/MS) calc. for C₁₅H₁₄ONa: 233.09369, found: 233.09368 [M+Na]⁺.

s-Peryllalcohol (9j):

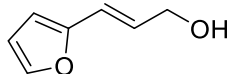


^1H -NMR (300 MHz, Methylene Chloride- d_2) δ 5.68 (s_{br}, 1H), 4.72 (s_{br}, 2H), 4.01 – 3.87 (m_{br}, 2H), 2.23 – 2.04 (m_{br}, 4H), 2.04 – 1.79 (m_{br}, 2H), 1.74 (s, 3H), 1.56 – 1.40 (m_{br}, 2H).

^{13}C -NMR (75 MHz, Methylene Chloride- d_2) δ 150.4 (C), 137.9 (C), 122.2 (CH), 108.6 (CH), 67.3 (CH₂), 41.6 (CH), 30.8 (CH₂), 27.9 (CH₂), 26.4 (CH₂), 20.9 (CH₃).

HRMS (ESI-TOF/MS) calc. for C₁₀H₁₇O, found: 153.12518 [M+H]⁺, calc. for C₁₀H₁₇ONa: 175.10934, found: 175.10934 [M+Na]

(E)-3-(furan-2-yl)prop-2-en-1-ol (9k):

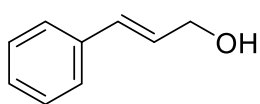


^1H -NMR (400 MHz, Methylene Chloride- d_2) δ 7.36 (s_{br}, 1H), 6.44 (dt, J = 16.0, 1.5 Hz, 1H), 6.39 (dd, J = 3.5, 2.0 Hz, 1H), 6.32 – 6.23 (m, 2H), 4.25 (s_{br}, 3H), 2.12 (s_{br}, 1H).

^{13}C -NMR (101 MHz, Methylene Chloride- d_2) δ 152.9 (C), 142.3 (CH), 128.0 (CH), 119.1 (CH), 111.6 (CH), 108.1 (CH), 63.2 (CH_2).

HRMS (ESI-TOF/MS) m/z calc. $\text{C}_7\text{H}_8\text{O}_2\text{Na}$ 147.04165, found: 147.04212 $[\text{M}+\text{Na}]^+$.

Cinnamyl alcohol (9l):

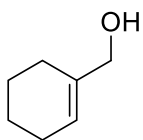


^1H -NMR (300 MHz, Chloroform- d) δ 7.45 – 7.19 (m, 5H), 6.68 – 6.57 (dt, $J = 16, 5.5$ Hz, 1H), 6.36 (dt, $J = 16, 5.5$ Hz, 1H), 4.32 (dd, $J = 5.5, 1.5$ Hz, 2H), 1.55 (s_{br} , 1H).

^{13}C NMR (75 MHz, Chloroform- d) δ 136.7 (C), 131.2 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 126.5 (CH), 63.8 (CH_2).

HRMS (EI) m/z calc. for $\text{C}_9\text{H}_{10}\text{O}$ 134.07262, found: 134.07269

1-Cyclohexen-1-methanol(9m):



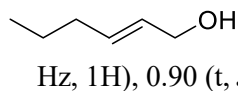
^1H -NMR (300 MHz, Methylene Chloride- d_2) δ 5.65 (m, 1H), 3.93 (d, $J = 4.0$ Hz, 2H), 2.06-1.95 (m, 4H), 1.69 – 1.53 (m, 5H), 1.44 (t, $J = 6$ Hz, 1H).

^{13}C -NMR (75 MHz, Methylene Chloride- d_2) δ 138.2 (C), 122.7 (CH), 67.7 (CH_2), 25.9 (CH_2), 25.3 (CH_2), 23.0 (CH_2), 22.9 (CH_2).

HRMS (EI) m/z calc. for $\text{C}_7\text{H}_{12}\text{O}$: 112.08827, found: 112.08828

Elemental analysis calc. (%) for $\text{C}_7\text{H}_{12}\text{O}$: C 74.95, H 10.78; found C 74.61, H 10.38

2-hexenol (9n):

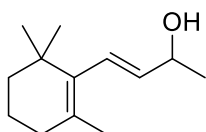


^1H -NMR (300 MHz, Chloroform- d) δ 5.75 – 5.58 (m, 2H), 4.09 (t_{br} , $J = 5.0$ Hz, 2H), 2.07-1.98 (m, 2H), 1.41 (h, $J = 7.5$ Hz, 2H), 1.25 (t, $J = 5.5$ Hz, 1H), 0.90 (t, $J = 7.7$ Hz, 3H).

^{13}C -NMR (75 MHz, Chloroform- d) δ 133.4 (CH), 129.1 (CH), 64.0 (CH_2), 34.4 (CH_2), 22.4 (CH_2), 13.8 (CH_3).

HRMS (EI) m/z calc. for $\text{C}_6\text{H}_{12}\text{O}$: 100.08827, found: 100.08828

β -Iononol(9o):



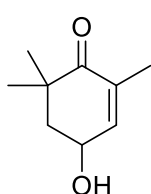
^1H -NMR (300 MHz, Chloroform- d) δ 6.10 – 5.99 (m, 1H), 5.49 (dd, $J = 16, 6.5$ Hz, 1H), 4.42-4.30 (m, 1H), 2.02 – 1.93 (t_{br} , $J = 6.0$ Hz, 2H), 1.66 (d, $J = 1.0$ Hz, 3H), 1.64 – 1.55 (m, 2H), 1.49 – 1.41 (m, 2H), 1.31 (d, $J = 6.5$ Hz, 3H), 0.98 (d, $J = 1.0$ Hz, 6H).

^{13}C -NMR (75 MHz, Chloroform-*d*) δ 137.7 (C), 136.7 (C), 128.9 (CH), 127.6 (CH), 69.6 (CH₂), 39.5 (CH₂), 34.0 (CH₂), 32.8 (CH₂), 28.8 (CH₃), 23.7 (CH₃), 21.5 (CH₃), 19.3 (CH₃).

HRMS (EI) *m/z* calc. for C₁₃H₂₂O: 194.16652, found: 194.16699

Elemental analysis calc. (%) for C₁₃H₂₂: C 80.35, H 11.41; found C 80.06, H 11.68

Isophorol (9p):

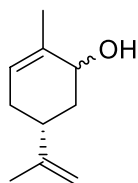


^1H -NMR (300 MHz, Methylene Chloride-*d*₂) δ 6.60 (m, 1H), 4.56 (s_{br}, 1H), 2.17 – 1.77 (m, 3H), 1.79 – 1.73 (dd, *J* = 2.0, *J* = 2.5 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 6H).

^{13}C -NMR (75 MHz, Methylene Chloride-*d*₂) δ 203.9 (CO), 146.6 (C), 133.8 (CH), 65.2 (CH), 47.0 (CH₂), 42.1 (C), 25.9 (CH₃), 24.6 (CH₃), 16.3 (CH₃).

HRMS (ESI-TOF/MS) calc for C₉H₁₅O: 155.10666, found: 155.0664 [M+H]⁺, calc. for C₉H₁₄O Na: 177.0886, found: 177.08858[M+Na]

Carveol (Main diastereomer)(9q):



^1H -NMR (300 MHz, Methylene Chloride-*d*₂) δ 5.55 – 5.39 (m, 1H), 4.71 – 4.61 (m, 2H), 4.18 – 3.87 (m, 1H), 2.33 – 1.76 (m, 5H), 1.70-1.63 (m, 6H), 1.62-1.56 (m_{br}, 1H).

^{13}C -NMR (75 MHz, Methylene Chloride-*d*₂) δ 149.6 (C), 136.8 (C), 123.9 (CH), 109.1 (CH₂), 71.1 (CH), 41.0 (CH), 38.6 (CH₂), 31.5 (CH₂), 20.7 (CH₃),

19.1 (CH₃).

HRMS (EI) *m/z* calc for C₁₀H₁₆O: 152.11957, found 152.11902

Elemental analysis calc. (%) for C₁₀H₁₆: C 78.90, H 10.59; found C 79.11, H 10.52

5.3. Chapter 2

5.3.1. Experimental procedures

General reaction procedure for the base-free transfer hydrogenation of esters

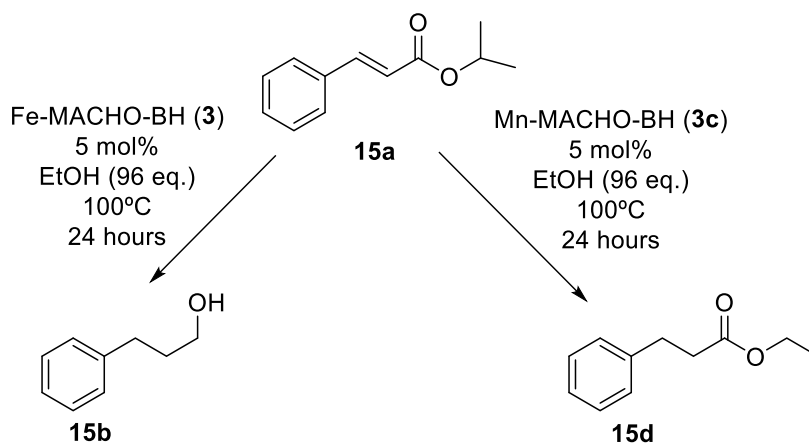
In an overnight dried 5 mL glass pressure tube equipped with a stirring bar, ester compound (0.5 mmol) was dissolved in EtOH (96 eq., 2800 μ L) under Argon atmosphere. When GC measurements were plan, dodecane as an internal standard was added (60 μ L). Right after, the addition of the Fe catalyst (5 mol%, 9.75 mg) was done. Afterwards, the tube was sealed with a teflon screw cap and covered from light with aluminium foil. The reaction was stirred vigorously for 24 hours at 100°C. After this time, the reaction tube was allowed to cool to room temperature. The obtained mixture was then filtered over a pad of silica to get rid of the catalyst and solvents were removed under reduced pressure. The resulting product was purified by flash column chromatography (SiO₂; cyclohexene: EtOAc, solvent ratio depends on the product).

For substrates **18a** and **26a**, EtONa (8.7 mg, 25 mol%) was added prior to the addition of the catalyst.

Finally, in order to monitor the progress of the reactions, a stainless steel autoclave provided with an auto sampler was used and reactions were scaled up 3 times. (For the rest, the procedure is identical to the described procedure).

Chemo selectivity observed in the transfer hydrogenation of **15a** by using different metal-based catalysts.

When the catalytic activity of Fe-MACHO-BH (**3**) was compared to the one of Mn-PNP-BH complex **3c**, different chemo-selectivities were observed (Scheme 3). Whereas the use of Fe catalyst **3** for TH of the α,β -unsaturated ester **15a** leads to the saturated alcohol **15b** with 71% of isolated yield, the use of Mn-PNP-BH leads to full conversion of **15a** to the saturated ethyl ester **15d**, under exactly the same reaction conditions (0.5 mmol of substrate, 96 eq. of EtOH, 5 mol% cat., at 100°C, covered from light, 24 hours reaction in a glass pressure tube). To the deep of our knowledge no Mn based catalyst is reported for the TH of activated olefins. However, optimizing reaction conditions on this transformation is out of the goal of this work.



Scheme E1. Different chemo selectivity in regard to catalyst used for the TH hydrogenation of the α,β -unsaturated ester compound **15a**

```

file      :D:\MSDCHEM\1\DATA\Ronald Alvaro\RAFT380_8.D
operator  : Ronald
acquired  : 31 Jan 2018  9:47      using AcqMethod RAFT1NEW.M
instrument : Instrument #1
sample Name: RAFT380_8
isc Info  :
file Number: 7

```

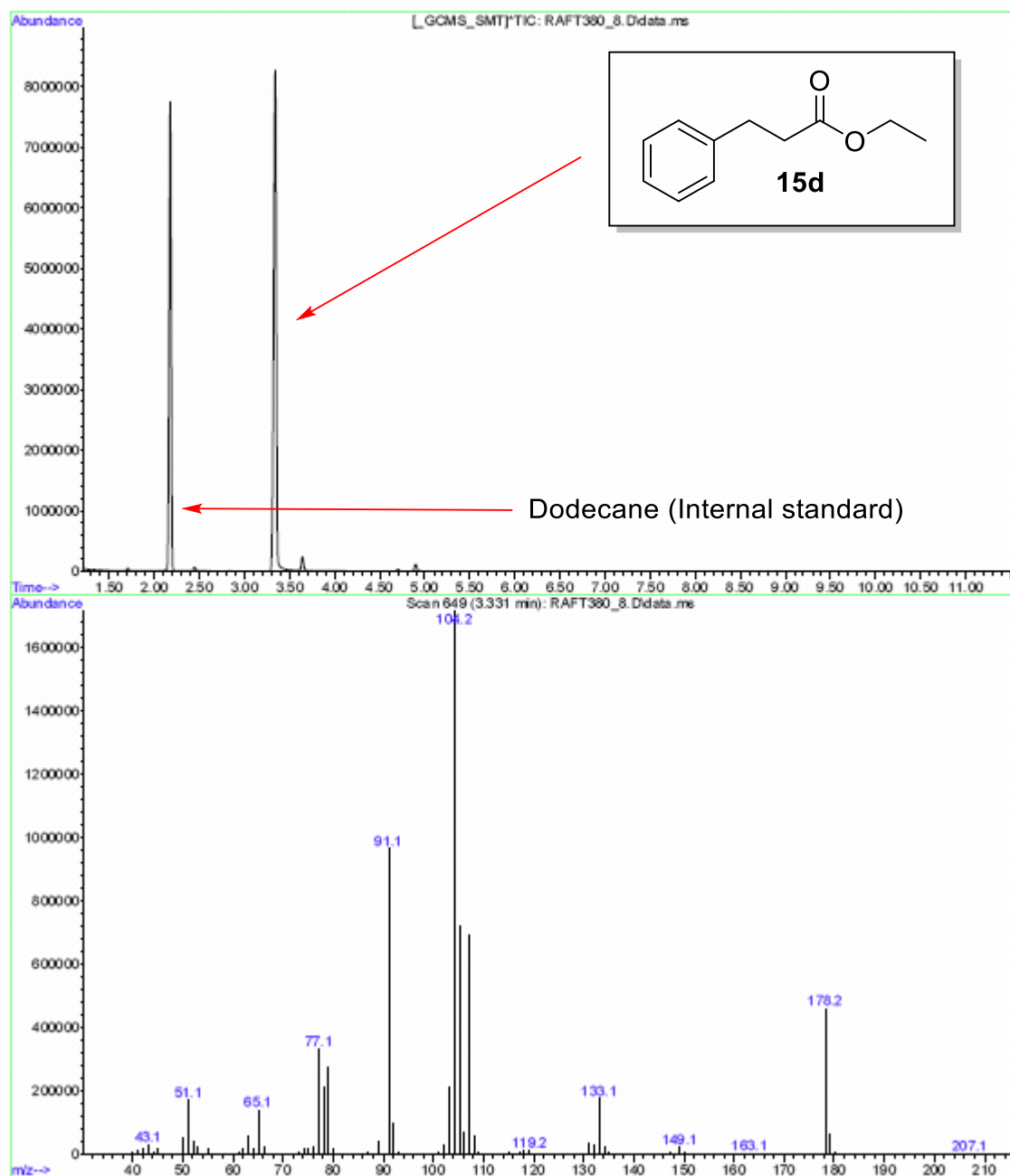
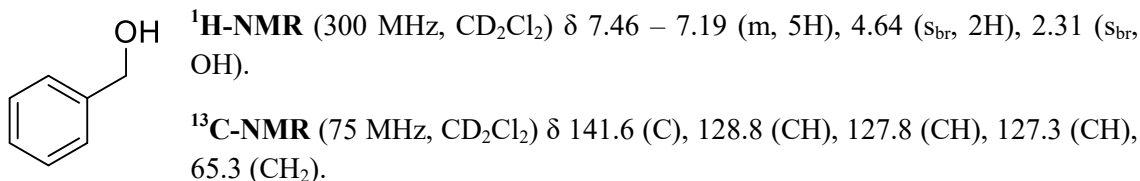


Figure E3. GC-Mass of the crude of the base-free Fe-catalysed transfer hydrogenation of isopropyl cinnamate (15a). Only one product is observed and fragmentation pattern fits with the one described in literature for 3-phenylpropanoate (15d). GC spectra is cut due to solvent delay program

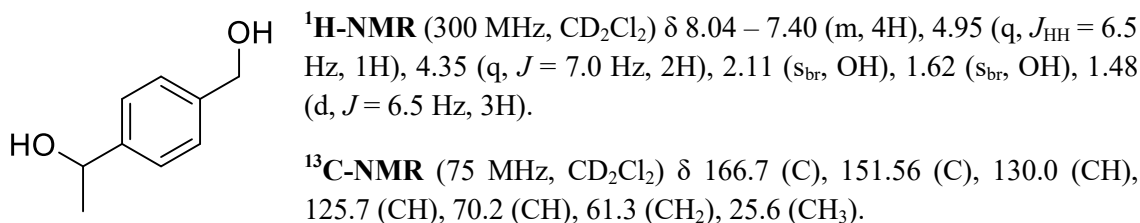
5.3.2. Analytical data

Benzyl alcohol (4b/5b/6b):

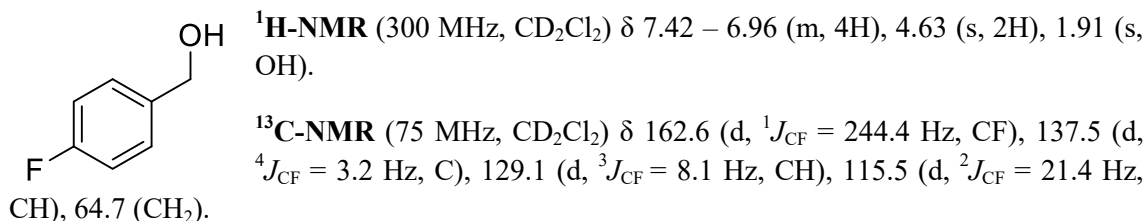


HRMS (EI) m/z calc. for C₇H₈O 108.05697, found: 108.05683

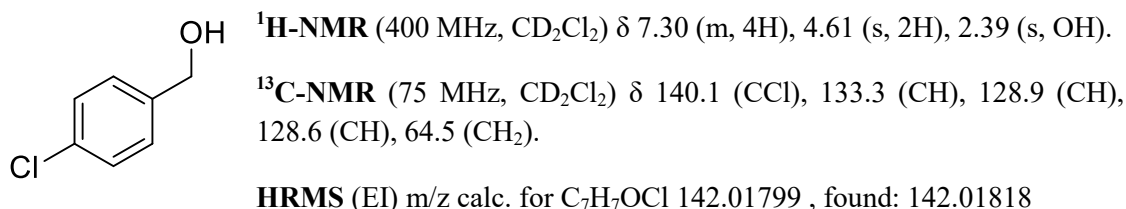
1-(4-(hydroxymethyl)phenyl)ethan-1-ol (7b):



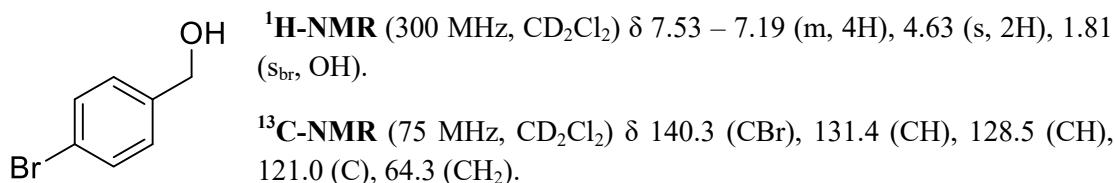
(4-fluorophenyl)methanol (8b):



(4-chlorophenyl)methanol (9b):

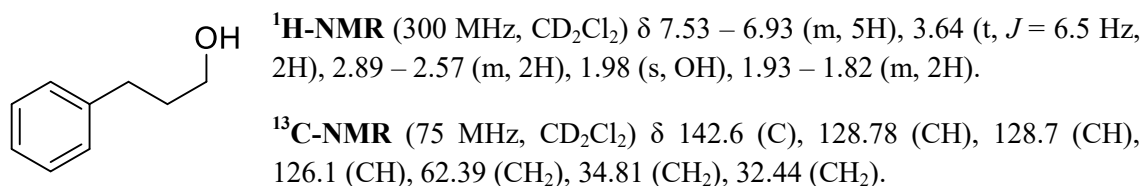


(4-bromophenyl)methanol (10b):



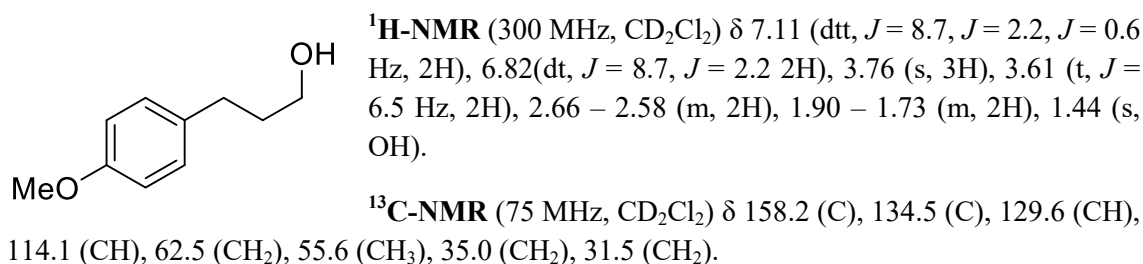
HRMS (EI) m/z calc. for C₇H₇OBr 185.96748, found: 185.96701

3-phenylpropan-1-ol (14b):



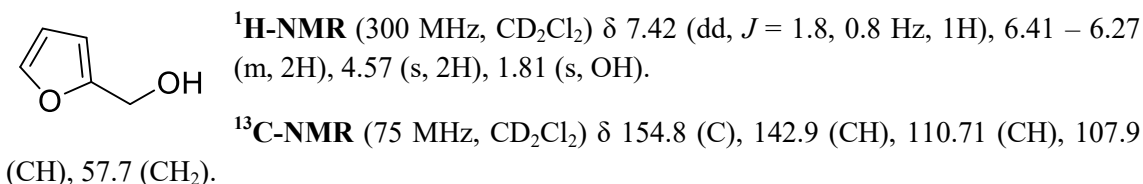
HRMS (EI) m/z calc. for C₉H₁₂O 136.08827, found: 136.08814

3-(4-methoxyphenyl)propan-1-ol (15b):



HRMS (EI) m/z calc. for C₁₀H₁₄O₂ 166.09883, found: 166.09920

furan-2-ylmethanol (16b):



HRMS (EI) m/z calc. for C₅H₆O₂ 98.03623, found: 98.03620

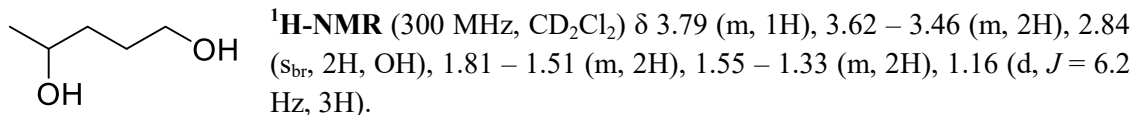
hexan-1-ol (17b):



(m, 1H), 1.46 (s_{br}, 1H, OH), 1.38 – 1.24 (m, 6H), 0.95 – 0.81 (m, 3H).

¹³C-NMR (75 MHz, CD₂Cl₂) δ 63.2 (CH₂), 33.3 (CH₂), 32.1 (CH₂), 25.9 (CH₂), 23.1 (CH₂), 14.2 (CH₃).

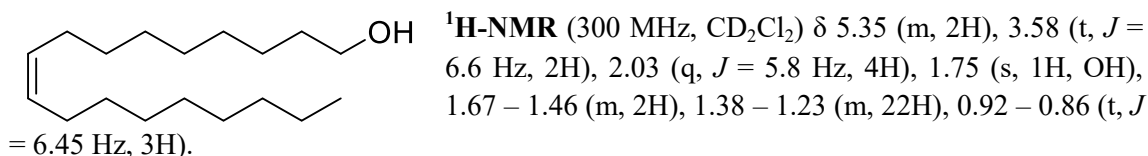
pentane-1,4-diol (18b/16b):



¹³C-NMR (75 MHz, CD₂Cl₂) δ 67.8 (CH), 62.7 (CH₂), 36.2 (CH₂), 29.2 (CH₂), 23.4 (CH₃).

GC-Mass (EI)(*m/z* +) theoretical fragmentation 100, 85, 75, 67, 56, 45, 41, 29. All found.

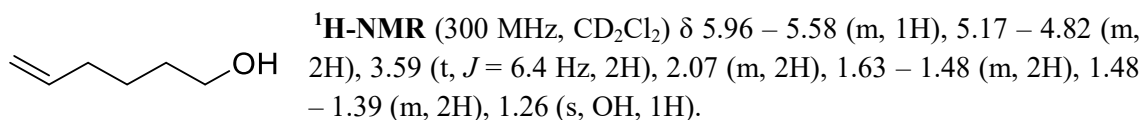
Oleyl alcohol (19b):



¹³C-NMR (75 MHz, CD₂Cl₂) δ 130.3 (CH), 130.2 (CH), 63.2 (CH₂), 33.4 (CH₂), 32.4 (CH₂), 30.6 (CH₂), 30.3 (CH₂), 30.2 (CH₂), 30.0 (CH₂), 30.0 (CH₂), 29.8 (CH₂), 29.8 (CH₂), 29.8 (CH₂), 27.7 (CH₂), 27.4 (CH₂), 26.3 (CH₂), 23.2 (CH₂), 14.4 (CH₃).

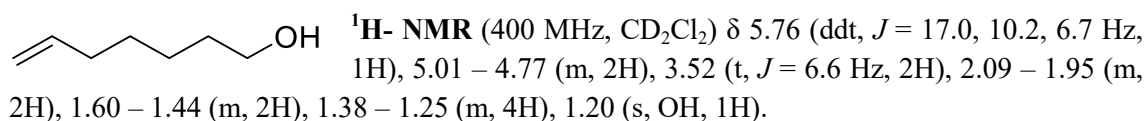
HRMS (EI) *m/z* calc. for C₁₈H₃₆O 268.27607, found: 268.27577

hex-5-en-1-ol (20b):



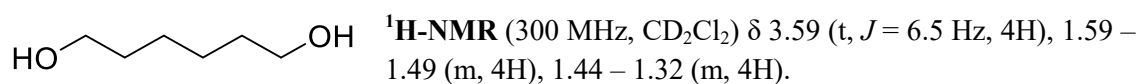
¹³C-NMR (75 MHz, CD₂Cl₂) δ 138.9 (CH), 114.2 (CH₂), 62.6 (CH₂), 33.5 (CH₂), 32.3 (CH₂), 25.1 (CH₂).

hept-6-en-1-ol (21b):



¹³C-NMR (101 MHz, CD₂Cl₂) δ 139.5 (CH), 114.4 (CH₂), 63.1 (CH₂), 34.1 (CH₂), 33.1 (CH₂), 29.1 (CH₂), 25.67 (CH₂).

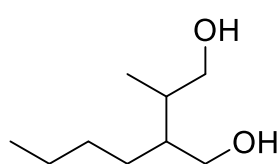
hexane-1,6-diol (22b/23b/24b):



¹³C-NMR (75 MHz, CD₂Cl₂) δ 53.8 (CH₂), 24.0 (CH₂), 16.7 (CH₂).

GC-Mass (detector **EI**) (m/z +) theoretical fragmentation 82,70,67, 57, 55, 54, 44,43, 42, 41, 39, 31, 29. All found

2-butyl-3-methylbutane-1,4-diol (25b):



Obtained as a mixture of isomers.

¹H-NMR (300 MHz, CD₂Cl₂) δ 3.79 (m, 2H), 3.62 – 3.46 (m, 3H), 2.84 (s_{br}, OH, 2H), 1.69 – 1.39 (m, 7H), 1.16 (d, *J* = 6.2 Hz, 6H).

¹³C-NMR (75 MHz, CD₂Cl₂) δ 75.3 (CH₂), 74.4 (CH₂), 60.1 (CH₂), 59.8 (CH₂), 36.0 (CH), 36.0 (CH), 35.6 (CH), 34.9 (CH), 33.7 (CH₂), 33.0 (CH₂), 28.3 (CH₂), 27.7 (CH₂), 22.4 (CH₂), 22.4 (CH₂), 15.9 (CH₃), 13.5 (CH₃), 13.3 (CH₃), 0.4 (CH₃).

5.4. Chapter 3

5.4.1. Experimental procedures

General procedure for catalyst activation

Inside a 45 mL stainless steel Parr autoclave the desired amount of catalyst was placed inside a 14 mL glass vial provided with a magnetic stirring bar, a teflon cap which was pierced with a needle to facilitate the gas exchange. Then the vial was closed, the autoclave was mechanically sealed and the atmosphere was replaced 3 times with N₂ to remove residual air and moisture. Right after, the atmosphere was again replaced 3 times with H₂ and finally the autoclave was pressurized with 30 bars of H₂ and stirred at 200 °C overnight. During this time, stirring was stopped and without cooling down the system 3 cycles of H₂ gas exchange were performed after which stirring was restarted. This protocol was repeated twice during catalyst activation to warrant removal of moisture. After that time, the stirring was stopped and the autoclave was allowed to cool down. The hydrogen atmosphere was exchanged again with nitrogen and the catalyst was left inside the autoclave without further opening.

General procedure for catalysis experiments

The substrate was distilled over PPh₃ (to remove peroxides) and K₂CO₃ and collected under Ar on molecular sieves. Then the 45 mL autoclave containing freshly activated catalyst was introduced inside the glove box together with a Schlenk tube containing the substrate. The autoclave was opened and the substrate was added via a Hamilton syringe to the vial containing the activated catalyst and a magnetic stirring bar. The vial was closed and placed again inside the autoclave. After closing hand-tied the autoclave inside the glove box, it was taken out and sealed mechanically. Right after, the atmosphere was exchanged 3 times with H₂ and pressurized with the desired hydrogen pressure and stirred on a preheated plate at 30°C. Reactions were monitored by H₂ pressure dropping. At the end of reaction the stirring was stopped, the autoclave atmosphere was exchanged with N₂ and the contents were filtered using a micro filter. Then, hexamethyl siloxane or dodecane as internal standard was added. Samples were taken for GC analysis and ¹H-NMR.

For the experiments described in Table 3 entries 5-8, freshly activated catalyst was transferred inside the glove box to an overnight dried 10mL schlenk flask provided with a magnetic stirring bar. Then 100μL (1mmol) of cyclohexene was added, the Schlenk tube was closed with a septum and the top was wrapped with electric tape to prevent atmospheric exchange. Then outside of the glove box, using the schlenk-line a vacuum was created inside the Schlenk tube and a balloon which was purged and filled with H₂ gas was connected via a needle. The reaction was stirred at room temperature. The reaction was monitored by taking samples that were filtered and diluted with iPrOH and analysed with GC.

For the monitoring of the reactions performed in the Amtech SPR16 (SLURRY PHASE REACTOR) catalyst activation was programmed digitally following the same schedule described for the 45 mL autoclave. After the activation stage the desired substrate was added via syringe under N₂ flow. Reaction conditions were also programmed digitally, similar as for the 45 mL autoclave, but the reaction was run under isobaric conditions in order to record the H₂ mass flow to monitor the reaction.

5.4.2. Analytical data and spectra

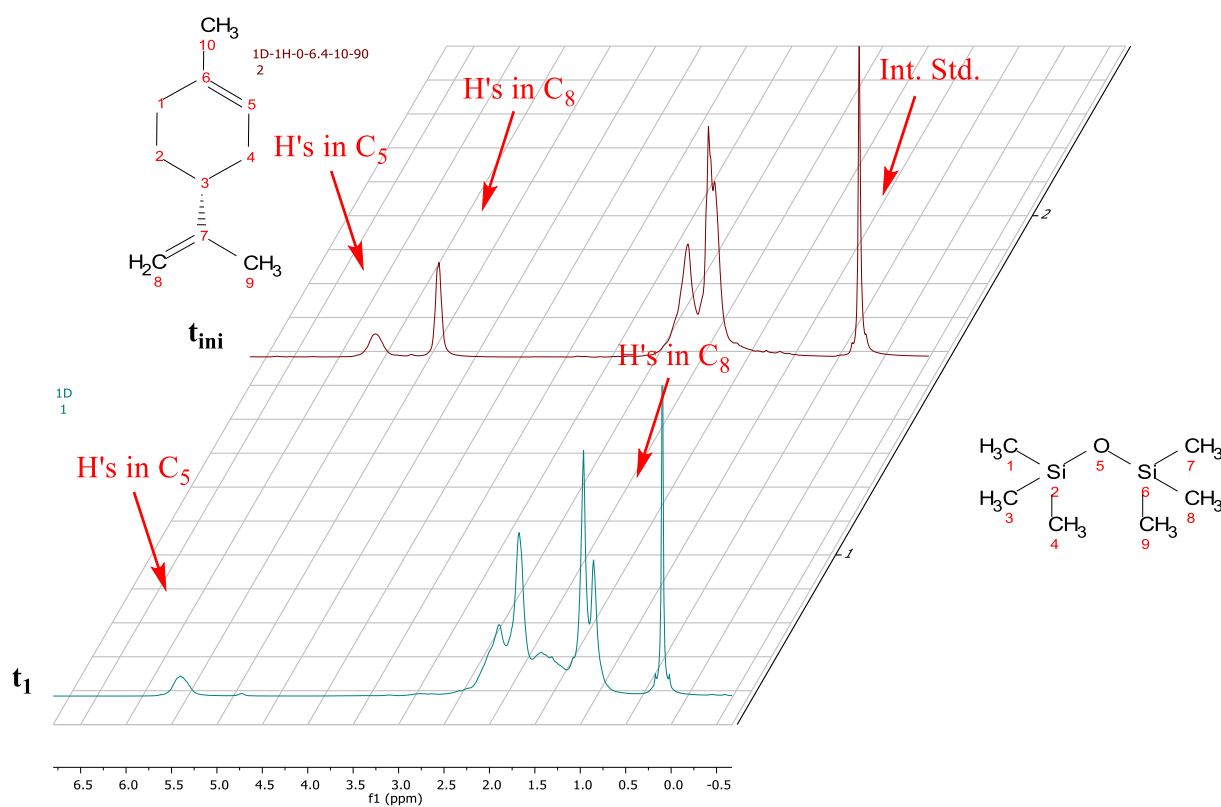


Figure E4. Example for determination of conversion yield and selectivity for Single Atom X in Table 4 entry 5.

6. References

- [1] S. Sorrell, J. Speirs, R. Bentley, A. Brandt, R. Miller, *Energy Policy* **2010**, *38*, 5290-5295.
- [2] a) *Top Value-Added Chemicals from Biomass Vol. I—Results of Screening for Potential Candidates from Sugars and Synthesis Gas*, ed. T. Werpy and G. Petersen, U. S. Department of Energy (DOE) by the National Renewable Energy Laboratory a DOE national Laboratory, **2004**; b) *Top value-Added Chemicals from Biomass Vol. II—Results of Screening for Potential Candidates from Biorefinery Lignin*, ed. J. E. Holladay, J. F. White, J. J. Bozell and D. Johnson, U. S. Department of Energy (DOE) by the Pacific Northwest National Laboratory, Richland, WA, US, PNNL-16983, **2007**; c) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411-2502; d) M. N. Belgacem, A. Gandini, *Monomers, Polymers and Composites from Renewable Resources*, Elsevier, **2008**; e) P. J. Deuss, K. Barta, J. G. de Vries, *Catal. Sci. Technol.* **2014**, *4*, 1174-1196; f) J. G. d. Vries, J. Deuss, K. Barta, in *Catalysis: Science, Technology, and Applications*, Royal Society of Chemistry, **2017**, pp. 29-73; g) V. Goldbach, P. Roesle, S. Mecking, *ACS Catal.* **2015**, *5*, 5951-5972; h) X. Li, P. Jia, T. Wang, *ACS Catal.* **2016**, *6*, 7621-7640.
- [3] J. O. Metzger, *Angew. Chem., Int. Ed.* **2006**, *45*, 696-698.
- [4] M. Jiang, Y. Xi, W. Dai, J. Zhang, R. Xu, K. Chen, P. Wei, Nanjing University of Technology, Peop. Rep. China . **2012**, p. 8pp.
- [5] A. S. H. Mohd, R. Abdulla, S. A. Jambo, H. Marbawi, J. A. Gansau, F. A. A. Mohd, R. Abdulla, K. F. Rodrigues, *Biochem Biophys Rep* **2017**, *10*, 52-61.
- [6] M. M. Bomgardner, in *c&en Chemical & Engineering news*, Vol. 92, 36, p.7, **2014**.
- [7] T. Levdivikova, (Ed.: L. The Market Publishers), (PRWEB) London, UK, <http://www.prweb.com/releases/2014/02/prweb11602185.htm>, **2017**.
- [8] J. Grub, E. Löser, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, **2000**.
- [9] a) J.-i. Ito, H. Nishiyama, *Tetrahedron Lett.* **2014**, *55*, 3153-3166; b) D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621-6686; c) B. Štefane, M. Wills, R. P. Herrera, D. C. Miller, L. Wang, Y. Obora, X. Ma, F. Perez, in *Hydrogen Transfer Reactions. Reductions and Beyond* (Eds.: G. Guillena, D. J. Ramón), Springer International Publishing, **2016**; d) A. Matsunami, Y. Kayaki, *Tetrahedron Lett.* **2018**, *59*, 504-513.
- [10] P. Pandey, I. Dutta, J. K. Bera, *Proc. Natl. Acad. Sci., India, Sect. A* **2016**, *86*, 561-579.
- [11] J. Zhou, *Appl. Catal., A* **2016**, *515*, 101-107.
- [12] S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201-2237.
- [13] a) P. A. Dub, T. Ikariya, *J. Am. Chem. Soc.* **2013**, *135*, 2604-2619; b) P. A. Dub, J. C. Gordon, *Dalton Trans.* **2016**, *45*, 6756-6781; c) P. A. Dub, J. C. Gordon, *ACS Catal.* **2017**, *7*, 6635-6655.
- [14] R. Cohen, C. R. Graves, S. T. Nguyen, J. M. L. Martin, M. A. Ratner, *J. Am. Chem. Soc.* **2004**, *126*, 14796-14803.
- [15] C. J. Kliewer, M. Bieri, G. A. Somorjai, *J. Am. Chem. Soc.* **2009**, *131*, 9958-9966.
- [16] L. Krähling, J. Krey, G. Jakobson, J. Grolig, L. Miksche, *Allyl Compounds*, **2000**.
- [17] C. Chapuis, D. Jacoby, *Appl. Catal., A* **2001**, *221*, 93-117.
- [18] R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675-5732.
- [19] M. T. Pirnot, D. A. Rankic, D. B. C. Martin, D. W. C. MacMillan, *Science* **2013**, *339*, 1593-1596.
- [20] A. Stolle, T. Gallert, C. Schmoeger, B. Ondruschka, *RSC Adv.* **2013**, *3*, 2112-2153.
- [21] a) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739; b) A. Shatskiy, T. Kivijaervi, H. Lundberg, F. Tinnis, H. Adolfsson, *ChemCatChem* **2015**, *7*, 3818-3821; c) J. Margalef, T. Slagbrand, F. Tinnis, H. Adolfsson,

References

- M. Dieguez, O. Pamies, *Adv. Synth. Catal.* **2016**, *358*, 4006-4018; d) I. Yamada, R. Noyori, *Org. Lett.* **2000**, *2*, 3425-3427; e) M. Hennig, K. Püntener, M. Scalone, *Tetrahedron: Asymmetry* **2000**, *11*, 1849-1858; f) J. A. Marshall, M. P. Bourbeau, *Org. Lett.* **2003**, *5*, 3197-3199; g) S. F. Lockwood, P. C. Tang, G. Nadolski, Z. Fang, Y. Du, W. Geiss, R. Williams, W. Burdick, M. Yang, Hawaii Biotech, Inc., Aiea, **2006**, p. 78 pp; h) M. Guo, D. Li, Y. Sun, Z. Zhang, *Synlett* **2004**, 741-743.
- [22] a) Z. Fang, M. Wills, *Org. Lett.* **2014**, *16*, 374-377; b) Z. Fang, M. Wills, *J. Org. Chem.* **2013**, *78*, 8594-8605; c) Z. Fang, G. J. Clarkson, M. Wills, *Tetrahedron Lett.* **2013**, *54*, 6834-6837; d) V. K. Vyas, R. C. Knighton, B. M. Bhanage, M. Wills, *Org. Lett.* **2018**, *20*, 975-978; e) D. J. Morris, A. M. Hayes, M. Wills, *J. Org. Chem.* **2006**, *71*, 7035-7044; f) D. Carmona, F. J. Lahoz, R. Atencio, L. A. Oro, M. P. Lamata, F. Viguri, E. San José, C. Vega, J. Reyes, F. Joó, Á. Kathó, *Chem. Eur. J.* **1999**, *5*, 1544-1564; g) L. Monnereau, D. Cartigny, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, *Chem. Eur. J.* **2015**, *21*, 11799-11806; h) Y.-C. Chen, T.-F. Wu, L. Jiang, J.-G. Deng, H. Liu, J. Zhu, Y.-Z. Jiang, *J. Org. Chem.* **2005**, *70*, 1006-1010; i) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 14960-14963; j) V. Parekh, J. A. Ramsden, M. Wills, *Catal. Sci. Technol.* **2012**, *2*, 406-414; k) J. Hannedouche, J. A. Kenny, T. Walsgrove, M. Wills, *Synlett* **2002**, 263-266; l) P. Peach, D. J. Cross, J. A. Kenny, I. Mann, I. Houson, L. Campbell, T. Walsgrove, M. Wills, *Tetrahedron* **2006**, *62*, 1864-1876.
- [23] a) S. Iyer, A. K. Sattar, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2003**, *42B*, 2805-2807; b) W. Baratta, K. Siega, P. Rigo, *Adv. Synth. Catal.* **2007**, *349*, 1633-1636; c) E. Putignano, G. Bossi, P. Rigo, W. Baratta, *Organometallics* **2012**, *31*, 1133-1142; d) B. Paul, K. Chakrabarti, S. Kundu, *Dalton Trans.* **2016**, *45*, 11162-11171; e) S. Baldino, S. Facchetti, A. Zanotti-Gerosa, H. G. Nedden, W. Baratta, *ChemCatChem* **2016**, *8*, 2279-2288; f) S. Baldino, W. Baratta, A. Blackaby, R. C. Bryan, S. Facchetti, V. Jurcik, H. G. Nedden, Johnson Matthey Public Limited Company, UK . **2016**, p. 112pp; g) T. Wang, X.-Q. Hao, X.-X. Zhang, J.-F. Gong, M.-P. Song, *Dalton Trans.* **2011**, *40*, 8964-8976.
- [24] a) C. A. Mebi, R. P. Nair, B. J. Frost, *Organometallics* **2007**, *26*, 429-438; b) F. Joo, A. Benyei, *J. Organomet. Chem.* **1989**, *363*, C19-C21; c) T. K. Bui, A. Arcelli, *Tetrahedron Lett.* **1985**, *26*, 3365-3368; d) H. Huo, Z. Zhou, A. Zhang, L. Wu, *Res. Chem. Intermed.* **2012**, *38*, 261-268; e) Z. Zhou, H. Huo, *Curr. Catal.* **2013**, *2*, 13-16; f) W. Bonrath, J. A. Medlock, B. Wuestenberg, J. Schuetz, T. Netscher, DSM IP Assets B. V., Herleen, **2015**, p. 32pp; g) B. T. Khai, A. Arcelli, *Tetrahedron Lett.* **1996**, *37*, 6599-6602; h) I. Szatmari, G. Papp, F. Joo, A. Katho, *Catal. Today* **2015**, *247*, 14-19.
- [25] X. Wu, X. Li, F. King, J. Xiao, *Angew. Chem., Int. Ed.* **2005**, *44*, 3407-3411.
- [26] a) B. R. James, R. H. Morris, *J. Chem. Soc., Chem. Commun.* **1978**, 929-930; b) S. N. Sluijter, C. J. Elsevier, *Organometallics* **2014**, *33*, 6389-6397; c) R. Wang, Y. Tang, M. Xu, C. Meng, F. Li, *J. Org. Chem.* **2018**, *83*, 2274-2281.
- [27] R. Wang, Y. Tang, M. Xu, C. Meng, F. Li, *The Journal of Organic Chemistry* **2018**, *83*, 2274-2281.
- [28] a) X. Wu, J. Liu, X. Li, A. Zanotti-Gerosa, F. Hancock, D. Vinci, J. Ruan, J. Xiao, *Angew. Chem., Int. Ed.* **2006**, *45*, 6718-6722; b) Y. Himeda, N. Onozawa-Komatsuzaki, S. Miyazawa, H. Sugihara, T. Hirose, K. Kasuga, *Chem. Eur. J.* **2008**, *14*, 11076-11081; c) Z. Zhou, Q. Ma, A. Zhang, L. Wu, *Appl. Organomet. Chem.* **2011**, *25*, 856-861; d) D. Talwar, X. Wu, O. Saidi, N. P. Salguero, J. Xiao, *Chem. Eur. J.* **2014**, *20*, 12835-12842; e) W. Wang, K. Ge, M. Bao, Dalian University of Technology, Peop. Rep. China, **2015**, p. 7pp; f) Z. Yang, Z. Zhu, R. Luo, X. Qiu, J.-t. Liu, J.-K. Yang, W. Tang, *Green Chem.* **2017**, *19*, 3296-3301.
- [29] Y.-M. Zhang, M.-L. Yuan, W.-P. Liu, J.-H. Xie, Q.-L. Zhou, *Org. Lett.* **2018**, *20*, 4486-4489.

- [30] a) T. N. Plank, J. L. Drake, D. K. Kim, T. W. Funk, *Adv. Synth. Catal.* **2012**, *354*, 597-601; b) T. W. Funk, A. R. Mahoney, R. A. Sponenburgh, K. P. Zimmerman, D. K. Kim, E. E. Harrison, *Organometallics* **2018**, *37*, 1133-1140; c) W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris, *Science* **2013**, *342*, 1080-1083; d) A. Bruneau-Voisine, D. Wang, V. Dorcet, T. Roisnel, C. Darcel, J.-B. Sortais, *Org. Lett.* **2017**, *19*, 3656-3659; e) R. Bigler, R. Huber, A. Mezzetti, *Angew. Chem., Int. Ed.* **2015**, *54*, 5171-5174; f) A. Mikhailine, R. H. Morris, P. O. Lagaditis, W. Zuo, University of Toronto, Can. . **2013**, p. 91pp; g) S. A. M. Smith, R. H. Morris, *Synthesis* **2015**, *47*, 1775-1779; h) A. Mikhailine, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2009**, *131*, 1394-1395; i) N. Meyer, A. J. Lough, R. H. Morris, *Chem. Eur. J.* **2009**, *15*, 5605-5610.
- [31] a) S. Iyer, A. K. Sattar, *Synth. Commun.* **1998**, *28*, 1721-1725; b) P. Phukan, A. Sudalai, *Synth. Commun.* **2000**, *30*, 2401-2405; c) G. Wienhoefer, F. A. Westerhaus, K. Junge, M. Beller, *J. Organomet. Chem.* **2013**, *744*, 156-159; d) M. Liu, F. Zhou, Z. Jia, C.-J. Li, *Org. Chem. Front.* **2014**, *1*, 161-166; e) S. Mazza, R. Scopelliti, X. Hu, *Organometallics* **2015**, *34*, 1538-1545; f) L. Jiang, T.-F. Wu, Y.-C. Chen, J. Zhu, J.-G. Deng, *Org. Biomol. Chem.* **2006**, *4*, 3319-3324.
- [32] a) H. Meerwein, R. Schmidt, *Justus Liebigs Ann. Chem.* **1925**, *444*, 221-238; b) A. Verley, *Bull. Soc. Chim. Fr.* **1925**, *37*, 537-542; c) W. Ponndorf, *Angew. Chem.* **1926**, *39*, 138-143; d) T. Nakano, S. Umano, Y. Kino, Y. Ishii, M. Ogawa, *J. Org. Chem.* **1988**, *53*, 3752-3757; e) Y. Hua, Z. Guo, H. Suo, X. Wei, *J. Organomet. Chem.* **2015**, *794*, 59-64; f) H.-F. Han, S.-F. Zhang, Z.-Q. Guo, H.-B. Tong, X.-H. Wei, *Polyhedron* **2015**, *99*, 71-76; g) Y. Hua, Z. Guo, H. Han, X. Wei, *Organometallics* **2017**, *36*, 877-883; h) H. Han, Z. Guo, S. Zhang, Y. Hua, X. Wei, *Polyhedron* **2017**, *126*, 214-219; i) C. F. de Graauw, J. A. Peters, H. van Bekkum, J. Huskens, *Synthesis* **1994**, 1007-1017; j) U. H. Dirk Klomp, Joop A. Peters, in *The Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2007**, pp. 585-630; k) C. R. Graves, E. J. Campbell, S. T. Nguyen, *Tetrahedron: Asymmetry* **2005**, *16*, 3460-3468; l) B. McNerney, B. Whittlesey, D. B. Cordes, C. Krempner, *Chem. Eur. J.* **2014**, *20*, 14959-14964.
- [33] a) N. Castellanos-Blanco, A. Arevalo, J. J. Garcia, *Dalton Trans.* **2016**, *45*, 13604-13614; b) H. Lundberg, H. Adolfsson, *Tetrahedron Lett.* **2011**, *52*, 2754-2758; c) T. Zweifel, J.-V. Naubron, T. Buttner, T. Ott, H. Grutzmacher, *Angew. Chem., Int. Ed.* **2008**, *47*, 3245-3249; d) W.-P. Liu, M.-L. Yuan, X.-H. Yang, K. Li, J.-H. Xie, Q.-L. Zhou, *Chem. Commun.* **2015**, *51*, 6123-6125.
- [34] J.-B. Sortais, V. Ritleng, A. Voelklin, A. Holuigue, H. Smail, L. Barloy, C. Sirlin, G. K. M. Verzijl, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, M. Pfeffer, *Organic Letters* **2005**, *7*, 1247-1250.
- [35] Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, *J. Am. Chem. Soc.* **1986**, *108*, 7400-7402.
- [36] H.-J. Knolker, E. Baum, H. Goesmann, R. Klauss, *Angew. Chem., Int. Ed.* **1999**, *38*, 2064-2066.
- [37] a) W. Kuriyama, T. Matsumoto, Y. Ino, O. Ogata, (WO 2011048727) Takasago International Corporation, Japan, **2011**; b) T. Touge, K. Aoki, H. Nara, W. Kuriyama, (WO 2012144650) Takasago International Corporation, Japan, **2012**; c) W. Kuriyama, T. Matsumoto, O. Ogata, Y. Ino, K. Aoki, S. Tanaka, K. Ishida, T. Kobayashi, N. Sayo, T. Saito, *Org. Process Res. Dev.* **2012**, *16*, 166-171.
- [38] a) R. Adam, E. Alberico, W. Baumann, H.-J. Drexler, R. Jackstell, H. Junge, M. Beller, *Chem. - Eur. J.* **2016**, *22*, 4991-5002; b) E. Balaraman, D. Milstein, *Top. Organomet. Chem.* **2015**, *48*, 19-43; c) J. Neumann, C. Bornschein, H. Jiao, K. Junge, M. Beller, *Eur. J. Org. Chem.* **2015**, *2015*, 5944-5948.

References

- [39] a) M. Nielsen, E. Alberico, W. Baumann, H.-J. Drexler, H. Junge, S. Gladiali, M. Beller, *Nature* **2013**, 495, 85-89; b) P. Sponholz, D. Mellmann, C. Cordes, P. G. Alsabeh, B. Li, Y. Li, M. Nielsen, H. Junge, P. Dixneuf, M. Beller, *ChemSusChem* **2014**, 7, 2419-2422.
- [40] a) M. Pena-Lopez, H. Neumann, M. Beller, *Chem. Commun.* **2015**, 51, 13082-13085; b) N. M. Rezayee, C. A. Huff, M. S. Sanford, *J. Am. Chem. Soc.* **2015**, 137, 1028-1031; c) C. Ziebart, R. Jackstell, M. Beller, *ChemCatChem* **2013**, 5, 3228-3231.
- [41] a) R. Corberan, E. Peris, *Organometallics* **2008**, 27, 1954-1958; b) A. Landwehr, B. Dudle, T. Fox, O. Blacque, H. Berke, *Chem. - Eur. J.* **2012**, 18, 5701-5714, S5701/5701-S5701/5714; c) S. Burling, M. K. Whittlesey, J. M. J. Williams, *Adv. Synth. Catal.* **2005**, 347, 591-594; d) J. Long, Y. Zhou, Y. Li, *Chem. Commun.* **2015**, 51, 2331-2334; e) L. Bagnell, C. R. Strauss, *Chem. Commun.* **1999**, 287-288; f) P. O. Lagaditis, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2011**, 133, 9662-9665.
- [42] L. Zhang, G. Raffa, D. H. Nguyen, Y. Swesi, L. Corbel-Demilly, F. Capet, X. Trivelli, S. Desset, S. Paul, J.-F. Paul, P. Fongarland, F. Dumeignil, R. M. Gauvin, *J. Catal.* **2016**, 340, 331-343.
- [43] H. Han, M. J. Krische, *Organic Letters* **2010**, 12, 2844-2846.
- [44] R. A. Farrar-Tobar, Z. Wei, H. Jiao, S. Hinze, J. G. de Vries, *Chem. Eur. J.* **2018**, 24, 2725-2734.
- [45] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. L. F. Ding, J. G. F. Egidi, A. P. B. Peng, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, N. R. J. Gao, W. L. G. Zheng, M. E. M. Hada, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. M. Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, *Gaussian Inc.: Wallingford, CT, USA* **2009**.
- [46] J. P. Perdew, *Physical Review B* **1986**, 33, 8822-8824.
- [47] A. Schäfer, C. Huber, R. Ahlrichs, *The Journal of Chemical Physics* **1994**, 100, 5829-5835.
- [48] P. J. Hay, W. R. Wadt, *The Journal of Chemical Physics* **1985**, 82, 299-310.
- [49] H. Jiao, K. Junge, E. Alberico, M. Beller, *J. Comput. Chem.* **2016**, 37, 168-176.
- [50] a) W. W. N. O, A. J. Lough, R. H. Morris, *Organometallics* **2011**, 30, 1236-1252; b) K.-N. T. Tseng, J. W. Kampf, N. K. Szymczak, *ACS Catal.* **2015**, 5, 5468-5485.
- [51] S. Chakraborty, P. O. Lagaditis, M. Forster, E. A. Bielinski, N. Hazari, M. C. Holthausen, W. D. Jones, S. Schneider, *ACS Catal.* **2014**, 4, 3994-4003.
- [52] a) J. G. de Vries, C. J. Elsevier, Editors, *Handbook of Homogeneous Hydrogenation, Volume 3*, Wiley-VCH Verlag GmbH & Co. KGaA, **2007**; b) P. Dupau, M.-L. Tran Do, S. Gaillard, J.-L. Renaud, *Angew. Chem., Int. Ed.* **2014**, 53, 13004-13006; c) G. Chelucci, S. Baldino, W. Baratta, *Acc. Chem. Res.* **2015**, 48, 363-379; d) M. Garbe, K. Junge, M. Beller, *Eur. J. Org. Chem.* **2017**, 2017, 4344-4362; e) G. A. Filonenko, P. R. van, E. J. M. Hensen, E. A. Pidko, *Chem Soc Rev* **2018**, 47, 1459-1483; f) E. Peris, R. H. Crabtree, *Chem. Soc. Rev.* **2018**, 47, 1959-1968; g) H. Valdes, M. A. Garcia-Eleno, D. Canseco-Gonzalez, D. Morales-Morales, *ChemCatChem* **2018**, Ahead of Print; h) S. Werkmeister, J. Neumann, K. Junge, M. Beller, *Chem. - Eur. J.* **2015**, 21, 12226-12250.
- [53] a) S.-H. Lee, G. I. Nikonov, *ChemCatChem* **2015**, 7, 107-113; b) A. Dubey, E. Khaskin, *ACS Catal.* **2016**, 6, 3998-4002.
- [54] a) A. Elisabetta, S. Peter, C. Christoph, N. Martin, D. Hans-Joachim, B. Wolfgang, J. Henrik, B. Matthias, *Angew. Chem., Int. Ed.* **2013**, 52, 14162-14166; b) C. Bornschein, S.

- Werkmeister, B. Wendt, H. Jiao, E. Alberico, W. Baumann, H. Junge, K. Junge, M. Beller, *Nat. Commun.* **2014**, *5*, 4111; c) M. Pena-Lopez, H. Neumann, M. Beller, *ChemCatChem* **2015**, *7*, 865-871.
- [55] D. H. Nguyen, X. Trivelli, F. Capet, J.-F. Paul, F. Dumeignil, R. M. Gauvin, *ACS Catal.* **2017**, *7*, 2022-2032.
- [56] A. Brzozowska, L. M. Azofra, V. Zubar, I. Atodiresei, L. Cavallo, M. Rueping, O. El-Sepelgy, *ACS Catal.* **2018**, *8*, 4103-4109.
- [57] a) T. Nishiguchi, K. Fukuzumi, *Bull. Chem. Soc. Jap.* **1972**, *45*, 1656-1660; b) G. Wienhoefer, F. A. Westerhaus, R. V. Jagadeesh, K. Junge, H. Junge, M. Beller, *Chem. Commun.* **2012**, *48*, 4827-4829; c) A. Lator, S. Gaillard, A. Poater, J.-L. Renaud, *Chem. Eur. J.* **2018**, *24*, 5770-5774.
- [58] a) S. Fu, N.-Y. Chen, X. Liu, Z. Shao, S.-P. Luo, Q. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 8588-8594; b) G. Zhang, Z. Yin, J. Tan, *RSC Adv.* **2016**, *6*, 22419-22423.
- [59] a) P. Yang, H. Xu, J. Zhou, *Angew. Chem., Int. Ed.* **2014**, *53*, 12210-12213; b) S. Guo, P. Yang, J. Zhou, *Chem. Commun.* **2015**, *51*, 12115-12117; c) S. Guo, J. Zhou, *Org. Lett.* **2016**, *18*, 5344-5347.
- [60] a) S. Elangovan, B. Wendt, C. Topf, S. Bachmann, M. Scalone, A. Spannenberg, H. Jiao, W. Baumann, K. Junge, M. Beller, *Adv. Synth. Catal.* **2016**, *358*, 820-825; b) T. vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Hoelscher, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* **2014**, *136*, 13217-13225; c) B. M. Stadler, P. Puylaert, J. Diekamp, R. van Heck, Y. Fan, A. Spannenberg, S. Hinze, J. G. de Vries, *Adv. Synth. Catal.* **2018**, *360*, 1151-1158.
- [61] F. S. Len Neufeld, Ruth Sheppard, Terry Gilman, *The New Plastics Economy. Rethinking the future of plastics*, World Economic Forum, **2016**.
- [62] J. M. Garcia, M. L. Robertson, *Science* **2017**, *358*, 870-872.
- [63] a) J. M. Garcia, *Chem.* **2016**, *1*, 813-815; b) B. Geyer, G. Lorenz, A. Kandelbauer, *EXPRESS Polym. Lett.* **2016**, *10*, 559-586.
- [64] a) J. A. Fuentes, S. M. Smith, M. T. Scharbert, I. Carpenter, D. B. Cordes, A. M. Z. Slawin, M. L. Clarke, *Chem. Eur. J.* **2015**, *21*, 10851-10860; b) E. M. Krall, T. W. Klein, R. J. Andersen, A. J. Nett, R. W. Glasgow, D. S. Reader, B. C. Dauphinais, S. P. McIlrath, A. A. Fischer, M. J. Carney, D. J. Hudson, N. J. Robertson, *Chem. Commun.* **2014**, *50*, 4884-4887; c) S. Westhues, J. Idel, J. Klankermayer, *Sci Adv* **2018**, *4*, eaat9669.
- [65] a) C. Chapuis, D. Jacoby, *Appl. Catal., A* **2001**, *221*, 93-117; b) R. G. Berger, *Flavours and Fragrances: Chemistry, Bioprocessing and Sustainability*, Springer GmbH, **2007**; c) J. Grub, E. Löser, Wiley-VCH Verlag GmbH & Co. KGaA, **2000**.
- [66] D. Srimani, A. Mukherjee, A. F. G. Goldberg, G. Leitus, Y. Diskin-Posner, L. J. W. Shimon, Y. Ben David, D. Milstein, *Angew. Chem., Int. Ed.* **2015**, *54*, 12357-12360.
- [67] a) K. V. N. S. Srinivas, I. Mahender, B. Das, *Synthesis* **2003**, 2479-2482; b) H. Firouzabadi, N. Iranpoor, B. Karimi, H. Hazarkhani, *Synlett* **2000**, 263-265.
- [68] a) J. Liu, *ACS Catal.* **2017**, *7*, 34-59; b) L. Liu, A. Corma, *Chem. Rev.* **2018**, *118*, 4981-5079; c) X. Cui, W. Li, P. Ryabchuk, K. Junge, M. Beller, *Nature Catalysis* **2018**, *1*, 385-397; d) A. Wang, J. Li, T. Zhang, *Nat. Rev. Chem.* **2018**, *2*, 65-81; e) B. Han, R. Lang, B. Qiao, A. Wang, T. Zhang, *Chin. J. Catal.* **2017**, *38*, 1498-1507; f) Boy Cornils, Wolfgang A. Herrmann, Matthias Beller, Rocco Paciello, *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Four Volumes. Third edition.*, Wiley-VCH Verlag GmbH & Co. KGaA, **2017**; g) J. D. A. Pelletier, J.-M. Basset, *Acc. Chem. Res.* **2016**, *49*, 664-677; h) S. Liang, C. Hao, Y. Shi, *ChemCatChem* **2015**, *7*, 2559-2567; i) C. Coperet, M. Chabanas, R. P. Saint-Arroman, J.-M. Basset, *Angew. Chem., Int. Ed.* **2003**, *42*, 156-181; j) H. Schwarz, *Catal. Sci. Technol.* **2017**, *7*, 4302-4314; k) B. C. Gates, M. Flytzani-Stephanopoulos, D. A. Dixon, A. Katz, *Catal. Sci. Technol.* **2017**, *7*, 4259-4275.

References

- [69] a) S. Anantharaj, M. Jayachandran, S. Kundu, *Chem. Sci.* **2016**, *7*, 3188-3205; b) J. He, W. Ji, L. Yao, Y. Wang, B. Khezri, R. D. Webster, H. Chen, *Adv. Mater.* **2014**, *26*, 4151-4155; c) Y. Zhang, X. Cui, F. Shi, Y. Deng, *Chem. Rev.* **2012**, *112*, 2467-2505; d) F. Shi, M. K. Tse, M.-M. Pohl, A. Brueckner, S. Zhang, M. Beller, *Angew. Chem., Int. Ed.* **2007**, *46*, 8866-8868.
- [70] S. Huebner, J. G. de Vries, V. Farina, *Adv. Synth. Catal.* **2016**, *358*, 3-25.
- [71] a) J. T. Yates, Jr., S. D. Worley, T. M. Duncan, R. W. Vaughan, *J. Chem. Phys.* **1979**, *70*, 1225-1230; b) R. B. Duarte, O. V. Safonova, F. Krumeich, J. A. van Bokhoven, *Phys. Chem. Chem. Phys.* **2014**, *16*, 26553-26560; c) J. Shan, M. Li, L. F. Allard, S. Lee, M. Flytzani-Stephanopoulos, *Nature* **2017**, *551*, 605-608; d) Y. Kwon, T. Y. Kim, G. Kwon, J. Yi, H. Lee, *J. Am. Chem. Soc.* **2017**, *139*, 17694-17699; e) J. C. Matsubu, V. N. Yang, P. Christopher, *J. Am. Chem. Soc.* **2015**, *137*, 3076-3084; f) T. K. Ghosh, N. N. Nair, *ChemCatChem* **2013**, *5*, 1811-1821; g) B. Zhang, H. Asakura, N. Yan, *Ind. Eng. Chem. Res.* **2017**, *56*, 3578-3587; h) S. Zhang, L. Nguyen, J.-X. Liang, J. Shan, J. Liu, A. I. Frenkel, A. Patlolla, W. Huang, J. Li, F. Tao, *Nature Commun.* **2015**, *6*, 7938; i) J. Tian, D. Yang, J. Wen, A. S. Filatov, Y. Liu, A. Lei, X.-M. Lin, *Nanoscale* **2018**, *10*, 1047-1055; j) L. Wang, W. Zhang, S. Wang, Z. Gao, Z. Luo, X. Wang, R. Zeng, A. Li, H. Li, M. Wang, X. Zheng, J. Zhu, W. Zhang, C. Ma, R. Si, J. Zeng, *Nat. Commun.* **2016**, *7*, 14036; k) R. Lang, T. Li, D. Matsumura, S. Miao, Y. Ren, Y.-T. Cui, Y. Tan, B. Qiao, L. Li, A. Wang, X. Wang, T. Zhang, *Angew. Chem., Int. Ed.* **2016**, *55*, 16054-16058.
- [72] a) L. Luo, H. Li, Y. Peng, C. Feng, J. Zeng, *ChemNanoMat* **2018**, *4*, 451-466; b) L. A. Oro, D. Carmona, *Vol. 1*, Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 3-30.
- [73] a) J. Pasel, S. Wohlrab, S. Kreft, M. Rotov, K. Loehken, R. Peters, D. Stolten, *J. Power Sources* **2016**, *325*, 51-63; b) Dongjing Liu, Radostina Dragomirova, Hanan Atia, Marga-Martina Pohl, Hadis Amani, Gabriele Georgi, Stefanie Kreft, Dominik Seeburg, Sebastian Wohlrab, *Submitted manuscript* **2018**.
- [74] J. Lian, J. Ma, X. Duan, T. Kim, H. Li, W. Zheng, *Chem. Commun.* **2010**, *46*, 2650-2652.
- [75] a) K. S. Khuong, W. H. Jones, W. A. Pryor, K. N. Houk, *J. Am. Chem. Soc.* **2005**, *127*, 1265-1277; b) F. R. Mayo, *J. Am. Chem. Soc.* **1953**, *75*, 6133-6141; c) F. R. Mayo, *J. Am. Chem. Soc.* **1968**, *90*, 1289-1295; d) P. J. Flory, *J. Am. Chem. Soc.* **1937**, *59*, 241-253.
- [76] a) V. V. Pushkarev, K. An, S. Alayoglu, S. K. Beaumont, G. A. Somorjai, *J. Catal.* **2012**, *292*, 64-72; b) G. A. Somorjai, J. Y. Park, *Top. Catal.* **2008**, *49*, 126-135.
- [77] D. Yang, P. Xu, N. D. Browning, B. C. Gates, *J. Phys. Chem. Lett.* **2016**, *7*, 2537-2543.
- [78] Y. Zhou, C. Jin, Y. Li, W. Shen, *Nano Today* **2018**, *20*, 101-120.
- [79] P. Hu, Z. Huang, Z. Amghouz, M. Makkee, F. Xu, F. Kapteijn, A. Dikhtiarenko, Y. Chen, X. Gu, X. Tang, *Angew. Chem., Int. Ed.* **2014**, *53*, 3418-3421.
- [80] H. Asakura, S. Hosokawa, T. Ina, K. Kato, K. Nitta, K. Uera, T. Uruga, H. Miura, T. Shishido, J.-y. Ohyama, A. Satsuma, K. Sato, A. Yamamoto, S. Hinokuma, H. Yoshida, M. Machida, S. Yamazoe, T. Tsukuda, K. Teramura, T. Tanaka, *J. Am. Chem. Soc.* **2018**, *140*, 176-184.
- [81] A. Corma, P. Serna, P. Concepcion, J. J. Calvino, *J. Am. Chem. Soc.* **2008**, *130*, 8748-8753.
- [82] H. Wei, X. Liu, A. Wang, L. Zhang, B. Qiao, X. Yang, Y. Huang, S. Miao, J. Liu, T. Zhang, *Nat. Commun.* **2014**, *5*, 5634.
- [83] a) G. Kyriakou, M. B. Boucher, A. D. Jewell, E. A. Lewis, T. J. Lawton, A. E. Baber, H. L. Tierney, M. Flytzani-Stephanopoulos, E. C. H. Sykes, *Science* **2012**, *335*, 1209-1212; b) F. Zhao, Y. Ikushima, M. Arai, *J. Catal.* **2004**, *224*, 479-483; c) B. Brandt, J.-H. Fischer, W. Ludwig, J. Libuda, F. Zaera, S. Schauermaann, H.-J. Freund, *J. Phys. Chem. C* **2008**, *112*, 11408-11420; d) M. D. Rossell, F. J. Caparros, I. Angurell, G. Muller, J. Llorca, M. Seco, O. Rossell, *Catal. Sci. Technol.* **2016**, *6*, 4081-4085.

- [84] C. Ravichandran, P. C. Badgujar, P. Gundev, A. Upadhyay, *Food Chem. Toxicol.* **2018**, *120*, 668-680.
- [85] G. Rubulotta, K. L. Luska, C. A. Urbina-Blanco, T. Eifert, R. Palkovits, E. A. Quadrelli, C. Thieuleux, W. Leitner, *ACS Sustainable Chem. Eng.* **2017**, *5*, 3762-3767.
- [86] S. Agarwal, J. N. Ganguli, *J. Mol. Catal. A: Chem.* **2013**, *372*, 44-50.
- [87] H. Kuno, M. Shibagaki, K. Takahashi, I. Honda, H. Matsushita, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1240-1243.
- [88] S. Ghosh, B. R. Jagirdar, *Dalton Trans.* **2017**, *46*, 11431-11439.
- [89] D. Wu, D. F. O'Shea, *Organic Letters* **2013**, *15*, 3392-3395.

7. Miscellaneous

7.1. Curriculum Vitae

PERSONAL DATA

Name and Surname: Ronald Alvaro Farrar Tobar
Address: Cavallers nº16, 2nd floor, pc 03700
City: Dénia (Alicante, Spain)
Telephone: +34694457969
Email: ronalfarrar@gmail.com
Date and place of birth: 14-05-1985 Dénia (Alicante, Spain).
Nationality: Spanish



ACADEMIC FORMATION

- PhD. Leibniz Institute for Catalysis (LIKAT-Rostock). (Germany, 2014 - 2018).
 - o Group of Catalysis with renewables & platform chemicals.
PhD Thesis: "Selective hydrogenation and transfer hydrogenation reactions".
With the supervision of Prof. Dr. Johannes G. de Vries.
- Official Master Degree in Organic Chemistry. Universitat de Barcelona (UB). (Spain, 2013 - 2014).
 - o Master Thesis: "Iminosugars synthesis".
Experimental project performed in the Research Unit in Asymmetric Synthesis of the Barcelona Science Park. (URSA-PCB).
With the supervision of Prof. Dr. Riera i Escalè, Antoni.
- Bachelor's degree in Chemistry. Universitat de Barcelona (UB). (Spain, 2008 - 2013).
 - o BS Thesis: "Divalent ligand synthesis approximation for avidin protein".
With the supervision of Dr. Farrera, Joan Antoni.
- Image. High-Level formative Course. I.E.S. Santa Eulàlia (Tarrassa, Spain 2006 - 2008).

PROFESIONAL EXPERIENCE

- UB Organic Dep. "*Fèlix Urpí & Pedro Romea group's*". Volunteer. (04/2013 - 06/2013).
 - o Functions: Starting Materials Synthesis.
- UB Organic Dep. Dr. Francisco López Calahorra's group. Volunteer. (07/2013)
 - o Functions: Starting Materials Synthesis.
- Analysis Laboratory. O.N.G. A.B.D.'s project "*Asociación para el bienestar y el desarrollo*". Volunteer. (02/2013 - 01/2014).
 - o Functions: Routine analysis using UV-Visible Spectrophotometry / T.L.C./ Colorimetric Tests
Direct collaboration with I + D searching cheap methodologies to identify and quantify different mixtures of substances.
- BASF Española S.L. Internship student in the quality control dep. (06/2013 - 09/2013).
 - o Functions: NIR calibration, general analytics using NIR, HPLC and titrations. Microbiology laboratory tasks.

LANGUAGES

- Spanish. Native.
- Catalán. Bilingual Competence.
- English. Fluent. Full Professional Competence.
- German. Basic level. Limited competence.

PUBLICATIONS

- de la Fuente A, Mena-Barragan T, Farrar-Tobar RA, Verdaguer X, Garcia Fernandez JM, Ortiz Mellet C, et al. "Stereoselective synthesis of 2-acetamido-1,2-dideoxynojirimycin (DNJNAc) and ureido-DNJNAc derivatives as new hexosaminidase inhibitors." *Org Biomol Chem.* **2015**;13(23):6500-10.
- Farrar-Tobar RA, Wei Z, Jiao H, Hinze S, de Vries JG. "Selective Base-free Transfer Hydrogenation of α,β -Unsaturated Carbonyl Compounds using iPrOH or EtOH as Hydrogen Source." *Chem - Eur J.* **2018**;24(11):2725-34
- Farrar-Tobar RA, Wozniak, B, Savini A, Hinze S, Tin S, de Vries JG. "Base-Free Iron Catalyzed Transfer Hydrogenation of Esters Using EtOH as Hydrogen Source." Manuscript submitted to *Angewandte Chem. Int. Ed.* (11/2018).

PARTICIPATION IN CONGRESSES

- "*EtOH as hydrogen source for selective transfer hydrogenation under base free conditions*". Poster in the "49. Jahrestreffen Deutscher Katalytiker." (Weimar, Germany. 04.2016)
- "*Base-free, selective transfer hydrogenation of unsaturated carbonyl compounds*". Talk in the "NCCC.The Netherlands' Catalysis and Chemistry Conference XVIII" (Noordwijkerhout, The Netherlands. 04.2017)
- "*Selective base-free transfer hydrogenation of α,β -unsaturated carbonyl compounds using i-PrOH and EtOH.*" Winner poster (to the most intelligible poster) in the "JungChemikerForum Poster party. Uni-Rostock." (Rostock, Germany 04.2017).
- "*Selective base-free transfer hydrogenation of unsaturated carbonyl compounds using EtOH and i-PrOH as hydrogen sources.*" Poster in the "OMCOS the 19th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis. (Jeju, South Korea. 06.2017)

OTHER LABOUR ACTIVITY

- **Homebuilding sector**
 - o Blacksmith trainee. Serrano Blacksmith's . (Dénia, Summer 2003).
- **Commercial sector**
 - o Partner capture. "*Médicos sin fronteras*" O.N.G. (Barcelona, Christmas campaign 2010).
- **Other Jobs**
 - o Storing and editing video data. "C.C.C.B." ("*Centre de Cultura Contemporànea de Barcelona*", 03/2008 - 06/2008).

OTHER INTERESTING DATA

- Domain of the most common software and applications required for research. (Chembiodraw, Mestre Nova, Sci finder, Office pack, etc).
- Very experienced with the schlenk techniques required for air and moisture sensitive transformations.
- Very experienced in organic synthesis and organometallic complex synthesis. From the set-up to the work up and product purification followed by the corresponding rigorous analysis by chromatographic and spectroscopic techniques.
- Highly problem-solving minded, good learning skills, analytic skills, social and communicative skills.
- Performing the tests from *16personalities.com* and *truity.com* gave as result ESTJ-A personality type.
- Highly motivated to keep on developing my skills, knowledge and career in organic synthesis, catalysis and their applicability in industry. However, I am open-minded and confident with a possible career change towards Technical Marketing.

REFERENCES

- **Prof. Dr. Romea, Pedro. Associate professor.** Organic chemistry dep. UB. Stereoselective Synthesis of Natural Products. Tel.+34 93 402 12 47 / pedro.romea@ub.edu
- **Prof. Dr. Riera i Escalè, Antoni. Full professor.** The Research Unit in Asymmetric Synthesis of the Barcelona Science Park. URSA. Tel. +34 93 40 37093 / antoni.riera@irbbarcelona.org
- **Prof. Dr. G. de Vries, Johannes. Head of department.** LIKAT. Catalysis with renewable resources & platform chemicals. Tel. +49(381)1281-384 / johannes.deVries@catalysis.de

7.2. Selbstständigkeitserklärung

Universität
Rostock
Dezernat 1
Referat 1.2

Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

Name Farrar Tobar, Ronald Alvaro
.....
(Name, Vorname)

Anschrift Cavallers n16, 2p PLZ 03700 Dénia (Alicante, Spanien)
.....
(Straße, PLZ, Wohnort)

Ich habe eine Dissertation zum Thema

SELECTIVE HYDROGENATION AND TRANSFER HYDROGENATION REACTIONS.....
.....

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock
angefertigt. Dabei wurde ich von Frau/Herrn

Prof. Dr. Johannes G. de Vries
.....
betreut.

Ich gebe folgende Erklärung ab:

1. Die Gelegenheit zum vorliegenden Promotionsvorhaben ist mir nicht kommerziell vermittelt worden. Insbesondere habe ich keine Organisation eingeschaltet, die gegen Entgelt Betreuerinnen/Betreuer für die Anfertigung von Dissertationen sucht oder die mir obliegenden Pflichten hinsichtlich der Prüfungsleistungen für mich ganz oder teilweise erledigt.
2. Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe. Dazu habe ich keine außer den von mir angegebenen Hilfsmitteln und Quellen verwendet und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen habe ich als solche kenntlich gemacht.

19.11.2018
Rostock, den

.....
(Unterschrift)