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Publication date:
2020

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Metal-Catalyzed Dehydrogenation of Alcohols

Ph.D. Thesis

Simone V. Samuelsen

Technical University of Denmark, Department of Chemistry

Supervisor: Professor Robert Madsen

Kongens Lyngby, 2020

Preface

This thesis describes the work conducted during my Ph.D. studies at the Department of Chemistry, the Technical University of Denmark from April 2017 to Marts 2020 under the supervision of Professor Robert Madsen.

The dissertation covers two projects regarding the development of new catalysts based on Earth-abundant transition metals for acceptorless dehydrogenation of alcohols. Two catalysts based on manganese and vanadium, respectively, have been described and studied.

Included in the three year Ph.D. study was 30.5 ECTS points of courses, 420 hours of dissemination, 170 hours of teaching and 170 hours membership of the Ph.D. committee, the latter two as department work. Additionally, a 2 months external stay at Haldor Topsøe A/S was conducted under the supervision of R&D director Esben Taarning and R&D manager Søren Tolborg.

So far, the presented work has led to one scientific publication published in the journal *Chemical Science*. A second publication is in preparation.

Acknowledgement

Before anyone else, I would like to thank my supervisor Professor Robert Madsen for giving me this great opportunity to be a part of his research group and work on such interesting projects in my pursuit to obtain a Ph.D. degree.

Thanks to all former and present members of the Madsen group. Especially thanks to Emilie, Samuel, Yulong, Bo and the Fabrizios for introducing me to a new field of chemistry, enjoyable company and nice conversations about anything and everything. Special acknowledgement goes to my favorite office- and labmate Eli, who devoted some of her precious time to give me feedback on my thesis. Furthermore, I would like to thank the students Mathias Børsting and Ahmad Chehaiber whose projects I supervised. You both did an amazing job.

A thousand thanks to all the rest of the people I have met here at DTU during the last three years. In particular, the people from our social group "The Strawberry Bros" and our lunch group "Pasta with olives". All of you always help enlighten even the darkest days. Although, my biggest and warmest thanks goes to Giorgia for being my no-doubt closets friend here at DTU.

I sincerely thank the technical staff of the Department of Chemistry for making everything work so easily. In particular thanks to Jette Nestén, Anne Hector, Johanne Nielsen, Marie Koefoed, Andreas Pedersen and Lars Bruhn.

I also want to thank Esben Taarning and Søren Tolborg for giving me the opportunity to carry out my external stay at Haldor Topsøe A/S.

Finally, great thanks goes to my family and friends outside DTU, who have always encouraged and supported me in my life decisions.

More than anything else, my most grateful thanks goes to my beloved boyfriend Martin, who was willing to move with me to Copenhagen, just so I could pursue my dreams, while our shared dreams were put on hold.

Kgs. Lyngby, 31th Marts 2020

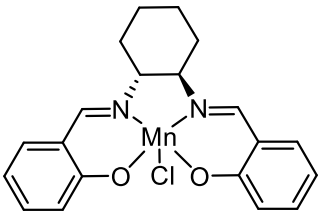
Simone V. Samuelsen

Abstract

This Ph.D. thesis describes the development of two novel catalysts based on Earth-abundant transition metals for acceptorless alcohol dehydrogenation to circumvent the use of traditional oxidants in organic synthesis.

Both catalysts mediate the dehydrogenative coupling of primary alcohols and amines into imines with only water and valuable hydrogen gas as by-products.

The first developed catalyst is the manganese(III) salen complex **19**, which constitutes the first example of a manganese(III) complex for acceptorless alcohol dehydrogenation. The reaction mechanism has been investigated by various practical experiments and theoretical calculations, and a metal-ligand cooperative pathway has been proposed.



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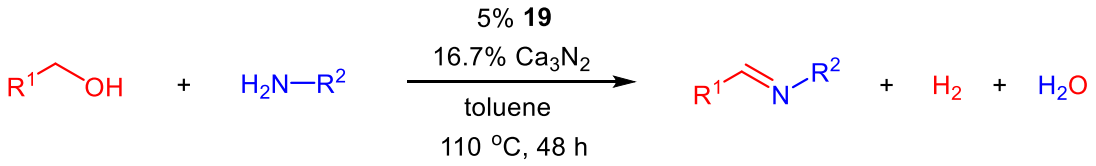
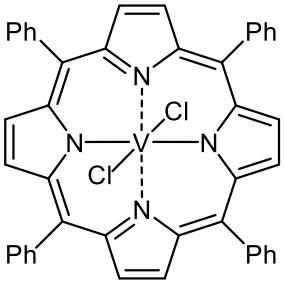


R^1 = alkyl
R^2 = alkyl, aryl

Scheme I: Dehydrogenative imine synthesis catalyzed by manganese(III) salen complex **19**.

The second developed catalyst is the vanadium(IV) porphyrin complex **48**, which is the first presented vanadium catalyst for acceptorless dehydrogenation of alcohols. The reaction mechanism has been investigated and is believed to involve the formation of a vanadium(IV) alkoxide complex, which degrades into the aldehyde and the corresponding vanadium(IV) hydride species. The aldehyde then reacts with the amine to produce the desired imine, whereas the vanadium(IV) hydride species react with another alcohol molecule to form hydrogen gas and regenerate the vanadium(IV) alkoxide complex.



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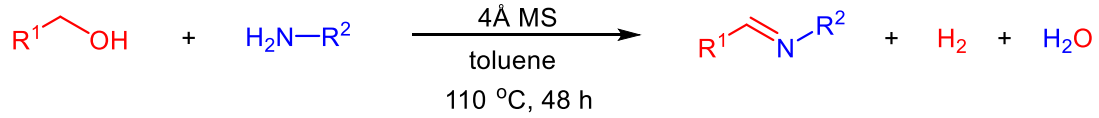


R^1 = alkyl
R^2 = alkyl, aryl

Scheme II: Vanadium-catalyzed dehydrogenative coupling of primary alcohols and amines into imines.

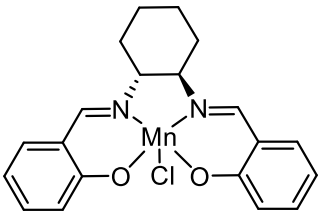
The thesis begins with three short chapters regarding the aim of the project as well as introduction to sustainability, catalysis and acceptorless alcohol dehydrogenation. Subsequently the development of the two novel catalysts are described and discussed in two chapters, followed by a conclusion on the entire project.

Resumé

Denne ph.d. afhandling omhandler udviklingen af to nye katalysatorer baseret på lettilgængelige overgangsmetaller til dehydrogenering i fravær af acceptorer for at undgå benyttelsen af traditionelle oxidanter i organisk syntese.

Begge katalysatorer formidler den dehydrogenative kobling af primære alkoholer og aminer til iminer kun med vand og værdifuld brint gas som biprodukter.

Den første udviklede katalysator er mangan(III) salen komplekset **19**, hvilket udgør det første eksempel på et mangan(III) kompleks til dehydrogenering af alkoholer i fravær af acceptorer. Reaktionsmekanismen er blevet undersøgt ved hjælp af diverse praktiske eksperimenter så vel som teoretiske beregninger, og en metal-ligand kooperativ mekanisme er blevet foreslået.



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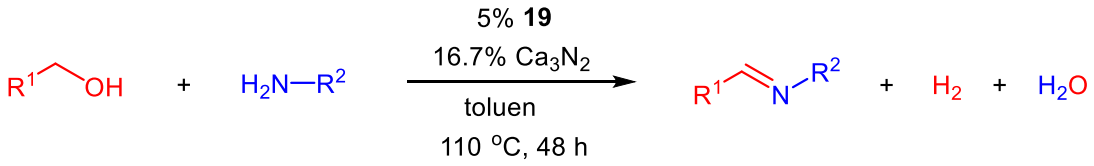
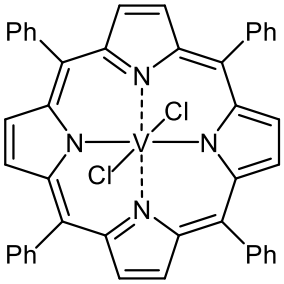


R^1 = alkyl
R^2 = alkyl, aryl

Skema I: Dehydrogenativ syntese af imin katalyseret af mangan(III) salen kompleks **19**.

Den anden udviklede katalysator er vanadium(IV) porphyrin komplekset **48**, hvilket er den første præsenterede vanadium katalysator til dehydrogenering af alkoholer i fravær af en acceptor. Reaktionsmekanismen er blevet undersøgt og formodes at involvere dannelsen af et vanadium(IV) alkoxid kompleks, som nedbrydes til et aldehyd og det korresponderende vanadium(IV) hydrid kompleks. Aldehydet reagerer derefter med aminen, som fører til dannelsen af den ønskede imin, mens vanadium(IV) hydrid komplekset reagerer med et nyt alkohol molekyle under dannelse af hydrogen gas med regenerering af vanadium(IV) alkoxid komplekset.



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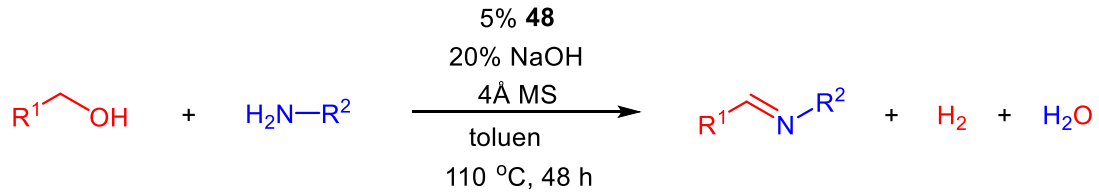


R^1 = alkyl
R^2 = alkyl, aryl

Skema II: Vanadium-katalyseret dehydrogenativ kobling af primære alkoholer og aminer for dannelse af iminer.

Afhandlingen indledes med 3 korte kapitler omhandlende projektets formål såvel som en introduktion til bæredygtighed, katalyse og dehydrogenering af alkoholer i fravær af acceptorer. Efterfølgende beskrives og diskuteres udviklingen af de to nye katalysatorer i to kapitler, efterfulgt af en samlet konklusion på hele projektet.

Abbreviations

AAD	Acceptorless alcohol dehydrogenation
AD	Acceptorless dehydrogenation
AE	Atom economy
BH	Borrowing hydrogen
bpnp	2,7-Bis(2-pyridyl)-1,8-naphthyridine
DMP	Dess-Martin Periodinane
E	Environmental factor
HAP	Hydroxyapatite
HQ	8-Quinolinate
IBX	2-Iodoxybenzoic acid
ICP-MS	Inductively coupled plasma mass spectrometry
KIE	Kinetic isotope effect
LOHC	Liquid organic hydrogen carrier
M	Metal
MCH	Methylcyclohexane
MLC	Metal-ligand cooperation
MS	Molecular sieves
TPP	Tetraphenylporphyrine
RDS	Rate-determining step
TOF	Turnover frequency
TPAP	Tetrapropylammonium perruthenate
TSPP	Tetra(*p*-sulfonatephenyl)porphyrine

For additional abbreviations, readers are referred to *JOC*'s list of standard abbreviations and acronyms: http://pubsapp.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf?

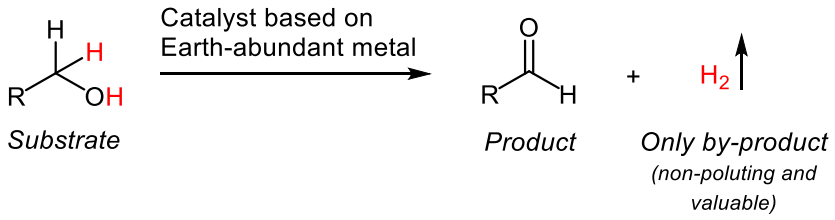
Table of Contents

1. Aim of project

The alcohol group is one of the main functional groups in organic chemistry. Chemical reactions involving alcohols include oxidation to carbonyl compounds as well as formation of ethers and olefins, which are reactions belonging to the core of organic synthesis. Traditionally, oxidation of an alcohol occurs in the presence of an inorganic oxidizing agent, which gives rise to a stoichiometric amount of toxic waste.

Due to today's challenge of sustainability, there is a strong interest in finding a way to circumvent this problem. This has led to the development of dehydrogenative reactions, where a metal catalyst removes hydrogen gas from an alcohol, producing the corresponding carbonyl group, which can subsequently undergo a variety of transformations into other functional groups such as amides, amines, imines, esters and carboxylic acids, depending on what other kind of substrate is added to the reaction. Everything is happening in the absence of an oxidant and the only by-product is valuable hydrogen gas.

Until recently, these dehydrogenative reactions have been catalyzed by catalysts based on metals from the platinum group such as ruthenium, iridium and rhodium. However, these precious metals suffer from both low global productions and high prices. As a result, it has become interesting to identify cheaper and more abundant metals with similar catalytic activities (Scheme **1.1**).



Scheme 1.1. Acceptorless dehydrogenation of primary alcohol catalyzed by Earth-abundant metals.

Accordingly, the purpose of this project is to develop novel and inexpensive catalysts based on Earth-abundant base metals for acceptorless dehydrogenative transformations of alcohols.

2. Introduction to catalysis

2.1 The challenge of sustainability and the beginning of green chemistry

In our everlasting search for better medicine, more effective crop protection and countless numbers of different commercial products, we unfortunately also started polluting and depleting our planet as well as causing harm to humans and animals. This is why, since the beginning of the 1980's, the word *sustainability* has been used more and more frequently. In short, sustainability means that we should pass on our planet to the next generation in the same condition, as when we received it.

In the chemistry society, the above-mentioned challenges lead to the introduction of the concept "Green chemistry". Green chemistry is among other things the development of ways to reduce waste, conserve energy, replace hazardous substances and use more renewable feedstocks. In 1998, Paul Anastas and John Warner developed the "12 Principles of Green Chemistry", which summaries the idea of what would make a chemical process greener (Figure **2.1**).[1] Today one of the most important goals in chemistry research is to develop green and sustainable synthetic methods.

Furthermore, the sustainability of a chemical reaction process can be evaluated through the use of green chemistry metrics. The two oldest and probably most common metrics' are the atom economy (AE)[2] and the environmental factor (E-factor).[3]

$$AE = \frac{Molecular\ weight\ of\ product}{Sum\ of\ molecular\ weights\ of\ reagents} * 100\%$$

$$E - factor = \frac{Total\ mass\ of\ waste}{Mass\ of\ final\ product}$$

The big difference between the two metrics' is that AE does not take additives, solvents and catalysts into account, which the E-factor does. On the other hand, AE is a fast and simple way to compare the sustainability of two reactions.

The 12 Principles of Green Chemsitry

1. Prevention - It is better to prevent waste than to treat or clean up waste after it has been created

2. Atom economy - Synthetic methods should be designed to maximize incorporation of all materials used in the process into the final product

3. Less Hazardous Chemical Syntheses - Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment

4. Designing Safer Chemicals - Chemical products should be designed to preserve efficiacy of function while reducing toxicity

5. Safer Solvents and Auxiliaries - The use of auxiliary substances should be made unnecessary wherever possible and, innocuous when used

6. Design for Energy Efficiency - Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure

7. Use of Reneawable Feedstocks - A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable

8. Reduce Derivatives - Unnecessary derivatization should be minimized or avoided if possible, because such steps require additional reagents and can generate waste

9. Catalysis - Catalytic reagnets are superior to stoichiometric reagents

10. Design for Degradation - Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment

11. Real-time analysis for Pollution Prevention - Analytical methodologies need to be further developed to allow for real-time, in-process montoring and control prior to the formation of hazardous substances

12. Inherently Safer Chemistry for Accident Prevention - Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires

Figure 2.1. The 12 Principles of Green Chemistry.[1]

Moving towards greener chemistry, at some point we should be able to pass on the planet to the next generation without concerns.

2.2 Catalysis

The 9th principle of green chemistry is catalysis. In chemical catalysis, a substance known as a catalyst is used to accelerate the rate of a chemical reaction by providing an alternative reaction pathway with a lower activation energy without affecting the overall Gibbs free energy of the reaction (Figure **2.2**). The catalyst itself is not consumed during the transformation. It works through a cyclic process consisting of different steps called a catalytic cycle, which means that the

catalyst can act repeatedly and be regenerated after the end of the reaction. Hence, in contrast to the use of stoichiometric reagents, which are a major source of waste, only a small amount of catalyst is required for a reaction.[4] Additionally, catalytic reactions often have low E-factors, are very atom economic and makes it possible to perform reactions efficiently that would maybe otherwise be impossible or very expensive. Today catalysts are a part of the production of 90% of all commercial products,[5] which gives a clear picture of the importance of catalysis.

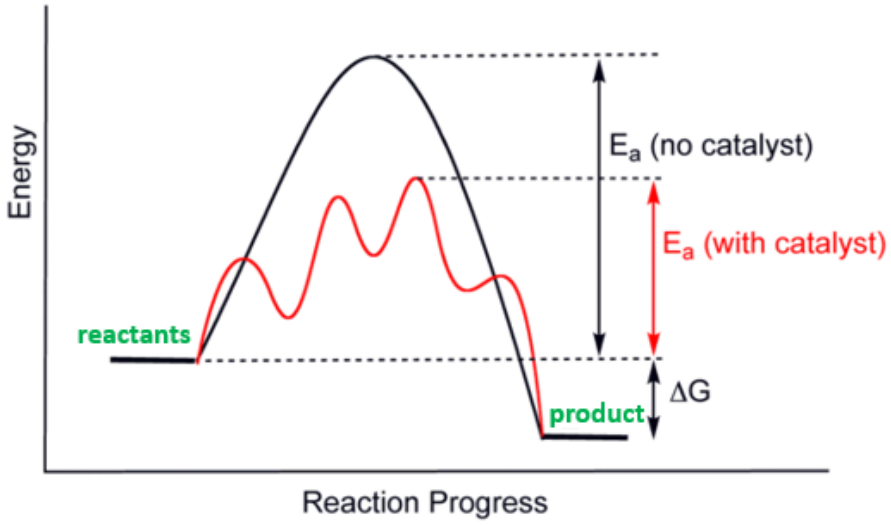
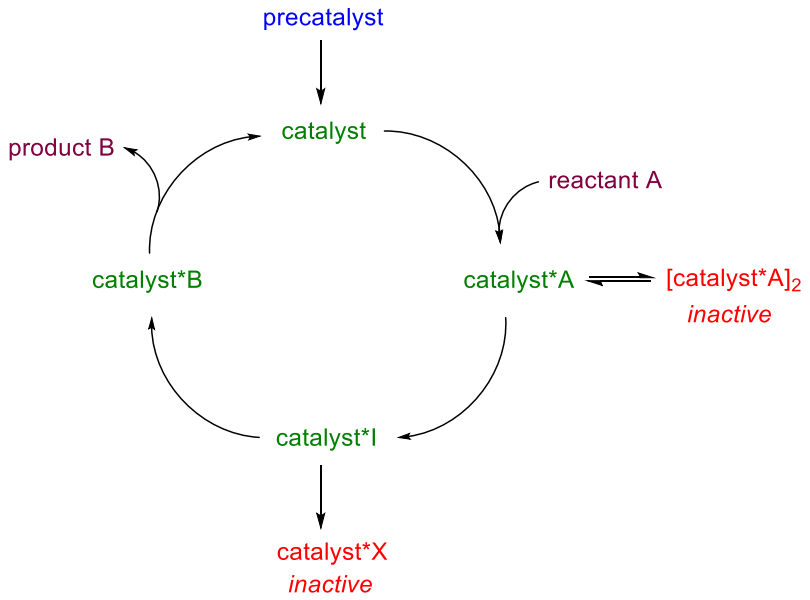


Figure 2.2. Potential energy diagram showing the effect of a catalyst in a chemical reaction.[6]

As mentioned above, a catalytic cycle is a multistep reaction mechanism, which is used to describe the role of a catalyst in the conversion of reactants into a desired product. Often a precursor to the catalyst, called a precatalyst, is used in the reactions. In the reaction mixture, the precatalyst is converted into the active catalyst. Precatalysts are normally more stable than the active catalysts, and therefore easier to handle. The catalyst activation is not a part of the actual cycle. The initial step in the catalytic cycle is the binding of one or more reactants to the catalyst, followed by a number of steps, leading to the release of the desired product and regeneration of the catalyst. Throughout the whole catalytic cycle, the active catalyst may be converted into inactive species, either reversibly or irreversibly. If the inactivation of the catalyst is reversible, the catalytic cycle will continue uninhibited, whereas the catalytic cycle will stop, if the inactivation is irreversible (Scheme **2.1**).



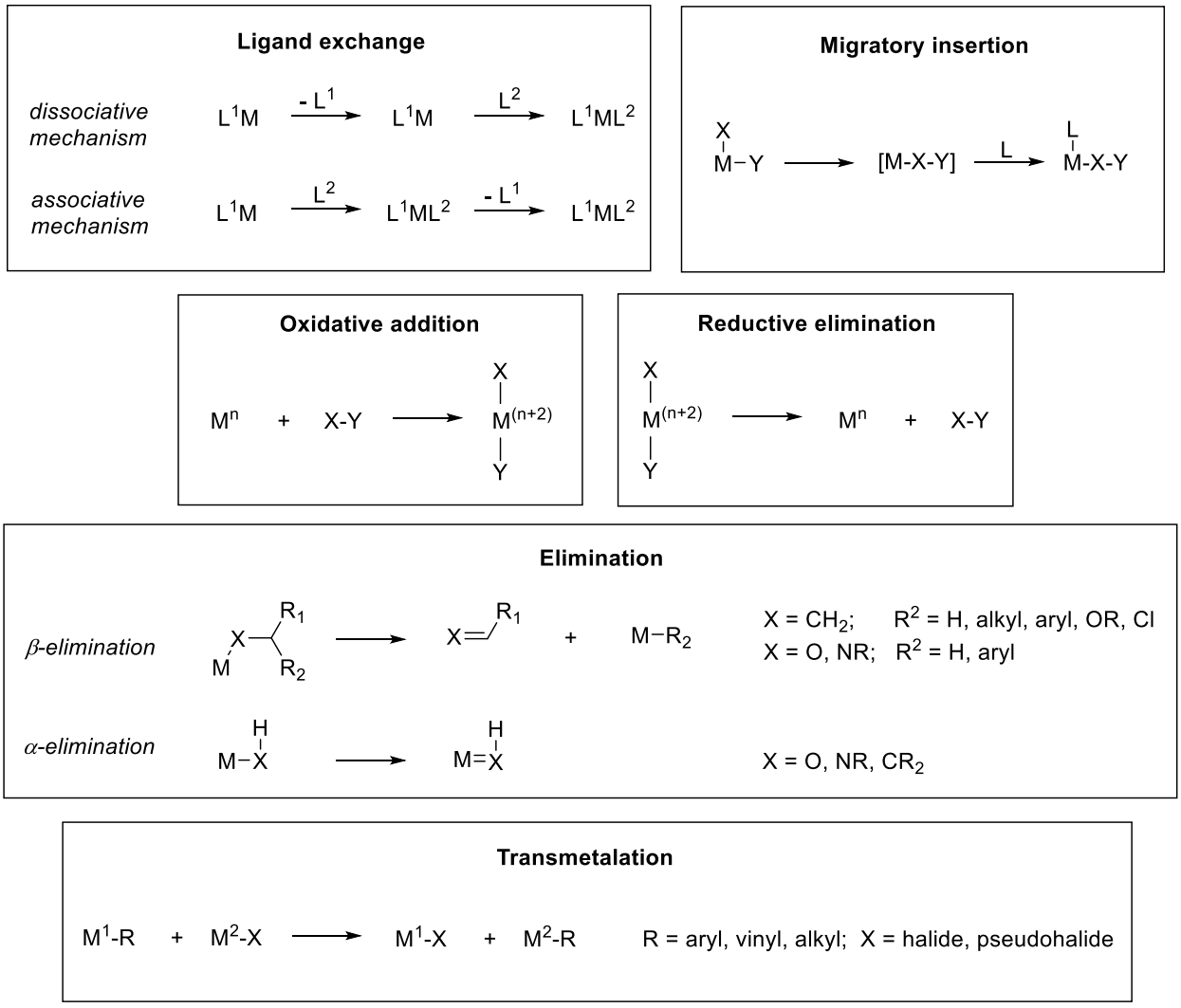
Scheme 2.1. Catalytic cycle for conversion of reactant A into product B through intermediate I.

Actually, the human kind has used catalysis for ages, e.g. by the use of yeast when making bread. Anyhow, the first reported example of catalysis used in the field of chemistry was performed by Gottlieb Kirchhoff in 1812, when he discovered the acid-catalyzed conversion of starch into sugar moieties.[7] At this point, this effect had no name, but in 1835, after various researchers had reported similar isolated observations by other compounds in different reactions, the term catalysis was introduced by Jöns Jacob Bérzelius.[8] However, the modern definition of catalysis as we know it today was presented by Wilhelm Ostwald in 1895.[9]

Catalysts can be classified as either homogeneous or heterogeneous. A homogeneous catalyst is in the same phase as the reactants, whereas a heterogeneous catalyst acts in a different phase than the reactants. One of the greatest advantages of heterogeneous catalysis is the ease of separation after end reaction, making it easy to reuse the catalyst. On the other hand, heterogeneous catalysts often suffer from limited activity and selectivity. Homogeneous catalysts are easily accessible for the reactants, promoting high catalytic activity as well as selectivity towards the desired product.[10] This is why, the development of homogeneous catalysts is continuously growing and it is estimated that 10-15% of the current catalytic processes in industry are homogeneous.[11] Additionally, catalysts can be classified in accordance to their structure. The most common types are organo-, photo and electrocatalysts as well as metal catalysts.

2.2.1 Metal catalysis

In metal catalysis, the catalyst consists of at least one metal, usually a transition metal, to which organic and/or inorganic ligands often are coordinated. Both the choice of metal and ligand is crucial for the catalyst efficiency for a certain reaction. During the catalytic cycle, the catalyst can undergo various transformations such as ligand exchange, oxidative addition, reductive elimination, migratory insertion, elimination and transmetalation (Scheme **2.2)**.[12] The ability of transition metals to access multiple oxidation states as well as their capability to coordinate substrates and thereby altering the reactivity of these, makes them excellent catalysts.

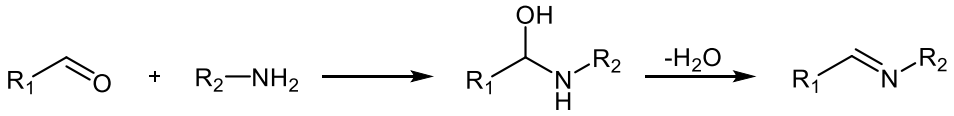


Scheme 2.2. Schematic presentation of common steps in catalytic cycle. M = Metal, L = Ligand.

3. Synthesis of imines by acceptorless alcohol dehydrogenation (AAD)

3.1 Imines

Imines are widely used as important intermediates in the synthesis of pharmaceutically and biologically active compounds, dyes, fragrances, fungicides and agricultural chemicals[13,14] as well as in a variety of organic transformations such as reduction, addition, condensation, cyclization and aziridination reactions in industrial synthetic processes.[13,15] Imines have the general formula R´RC=NR´´. If R´´ is not a hydrogen atom, the imine functionality is known as a Schiff base, which was discovered and named by Hugo Schiff in 1864.[16] The presence of a lone pair of electrons on the nitrogen atom of an imine group facilitates coordination to various metals, making molecules containing imine groups feasible ligands in homogeneous catalysis.[13] Because of the diverse applications of imines, research in the field of imine synthesis remains one of the major and important topics in organic synthesis.[13,15] Most commonly, imines are prepared by the condensation of amines with carbonyl compounds (Scheme **3.1**) as originally reported by Schiff.[16] This reaction proceeds by a nucleophilic addition of the amine nitrogen to the carbonyl carbon to give a hemiaminal intermediate followed by elimination of water, yielding the imine. This procedure has been reported for the synthesis of various imines, where neither catalyst, additive nor solvent are needed.[17,18]



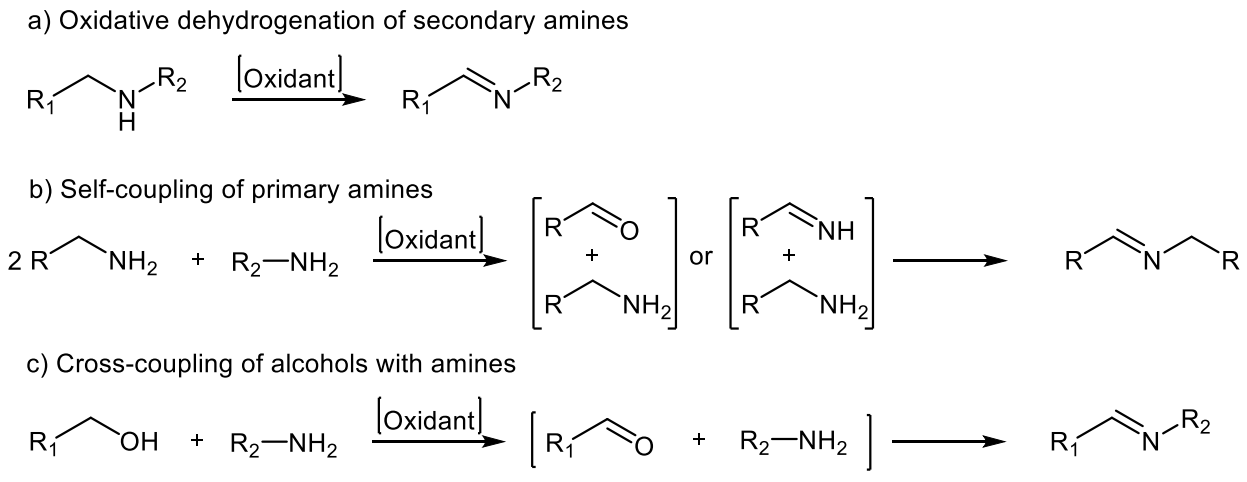
Scheme 3.1. Traditional method to synthesize imines.

The problem with the traditional imine synthesis procedure is that it often involves unstable aldehydes and that the equilibrium usually favors the reverse reaction. This means that azeotropic distillation by Dean-Stark apparatus together with the use of catalysts acting as Lewis acids to catalyze the nucleophilic attack of the amine and/or dehydrating agents are usually needed to push the reaction in the forward direction. In addition, the reaction of aliphatic aldehydes and amines

does not necessarily lead to the desired imine. Moreover, ketones react with amines slowly and often require harsh reaction conditions. In general, the traditional procedure is limited to the reaction between highly nucleophilic amines and strongly electrophilic aldehydes/ketones.[13] Therefore, the development of an alternative, efficient and sustainable procedure with a broad scope of imine products is highly appealing because of environmental concerns.

3.2 Synthesis of imines from catalytic oxidations of primary alcohols and/or amines

Since Hugo Schiff's discovery, several other methods to synthesize imines have been developed. These methods include hydroamination of alkynes with amines,[19] hydrogen transfer from amines to alkynes,[20] reductive imination of nitro compounds,[21] addition of organometallic reagents to nitriles,[22] decarboxylative amine coupling,[23] arylation of nitriles,[24] addition of arenes or boronic acids to nitriles,[25] coupling of aldimines with boronates,[26] reduction of secondary amides,[27] coupling of aryl halides with isonitriles and organometallic reagents,[28] coupling of aldehydes with alkyl bromides and ammonia,[29] addition of isocyanides to electron-rich arenes,[30] coupling of gem-dibromomethylaryl compounds and primary amines,[31] aza-Wittig reaction and coupling of vinyl bromide with amines.[32] However, especially three approaches have gained a lot of attention; (a) oxidative dehydrogenation of secondary amines, (b) oxidative self-coupling of primary amines, and (c) oxidative cross-coupling of alcohols with amines (Scheme **3.2**).



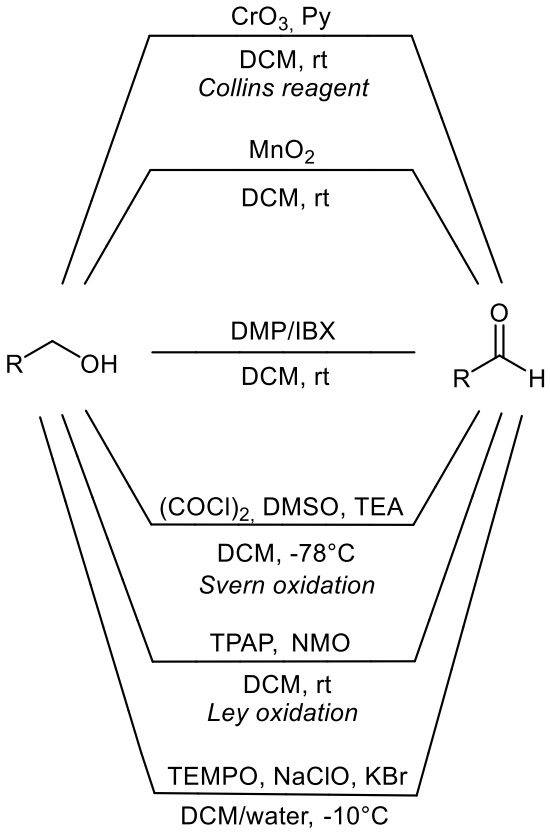
Scheme 3.2. New approaches to synthesize imines by oxidation of alcohols and amines.

The oxidative dehydrogenation of secondary amines offers high selectivity, since the substrates cannot be further dehydrogenated into e.g. nitriles. Yet, the efficiency of the substrate conversion is affected by the steric hindrance around the N-H bond and more importantly, no new C-N bond is formed, which the two other methods shown in Scheme **3.2** offer.[15] In 1933, the dehydrogenation of amines to give imines was reported by Ritter.[33] Homo-coupled imines from the self-coupling of primary amines are easily obtained, whereas hetero-coupled imines are less accessible. Additionally, there is the risk of transformation of the primary amine into nitrile, amide or azo compound by-products because of the possibility of over-oxidation if an oxidant is present in the reaction.

In 1909, Sabatier reported the direct *N*-alkylation of amines with alcohols to produce secondary amines as the final products with imines as intermediates.[34] Later, this approach has been used to the selective synthesis of the imine product. The advantages of the cross-coupling of alcohols with amines is that both symmetric and unsymmetric imines can be readily synthesized by choosing different starting materials. Additionally, the unstable aldehydes are avoided as starting materials, which is also the case of the two other approaches shown in Scheme **3.2**. On the other hand, alcohols are desirable starting materials because they are inexpensive, easily available by various industrial processes and can be procured renewably via fermentation or catalytic conversion of lignocellulose.[14] Lignocellulose is an abundantly available biomass and therefore a suitable non-fossil carbon source. Consequently, it is considered to be of high importance to develop catalytic reactions for synthesizing different compounds from alcohols to reduce CO_2 emissions and save fossil carbon feedstock. Hence, this procedure fulfills the 7th principle "use of renewable feedstocks" of the 12 principles of green chemistry (Figure **2.1**). Therefore, the cross-coupling of alcohols with amines is considered an environmentally benign protocol.

The biggest drawback with this approach is that alcohols are quite unreactive. They are poor leaving groups, meaning that they often have to be converted into better leaving groups by e.g. protonation, sulfonation or halogenation to be able to participate in different reactions. These approaches have some issues. The acidic environment that is required for protonation of the alcohol may also protonate and thereby deactivate the incoming nucleophile (especially amines), and many alkyl sulfonates and alkyl halides are known to be mutagenic.[35] For this reason, several chemical transformations would be more environmentally friendly and efficient if better ways of

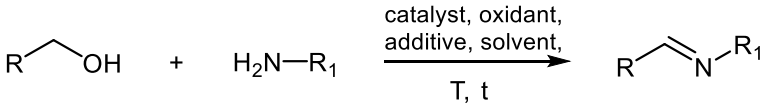
making alcohols more reactive existed. A possible solution is to oxidize the alcohol into the corresponding more reactive carbonyl group. In this case, the major challenge is the selective oxidation of the alcohol into the corresponding intermediate aldehyde or ketone under mild conditions. Traditional methods to oxidize alcohols into aldehydes use stoichiometric or excess amounts of inorganic oxidants in addition to employing various additives and cocatalysts, e.g. $CrO_3{\bullet}Py_2$ (Collins reagent),[36] Dess-Martin Periodinane (DMP),[37] 2-iodoxybenzoic acid (IBX), MnO_2,[38] activated DMSO (Svern oxidation),[39] tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) (Ley oxidation)[40] and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)/NaOCl (Scheme **3.3**),[41,42] leading to the generation of a copious stoichiometric amount of often toxic waste, which is not desirable if the goal is an environmentally and economically benign protocol. Furthermore, these conditions are also able to oxidize the amine starting material,[43,44,45] leading to undesirable by-products, as was the case with the self-coupling of amines.



Scheme 3.3. Traditional methods for the oxidation of primary alcohols into aldehydes with stoichiometric oxidants.

Because of the above-mentioned challenges, a wide range of catalysts have been developed for these transformations during the past years. The associated catalysts include among others transition metal, photo-, electro- and organocatalysts. In the case of photo-,[46–49] electro-[50,51] and organocatalysts[52–55] mainly amine oxidation has been shown to work with few exceptions.[56] Additionally, a co-catalyst based on transition metals are often needed as well. On the other hand, various transition metals have been shown to catalyze the oxidative coupling of amines and alcohols in the presence of an environmentally friendly and cheap oxidant (air/O_2) such as Mn,[57,58] Au,[59,60] Pd,[61–63] Pt,[64] Cu,[65–68] V,[69] Ag[70,71] and Fe.[72] Some examples are shown in Table **3.1**.

Table 3.1. Various catalysts used in the oxidative cross-coupling of alcohols with amines in presence of mild oxidants.

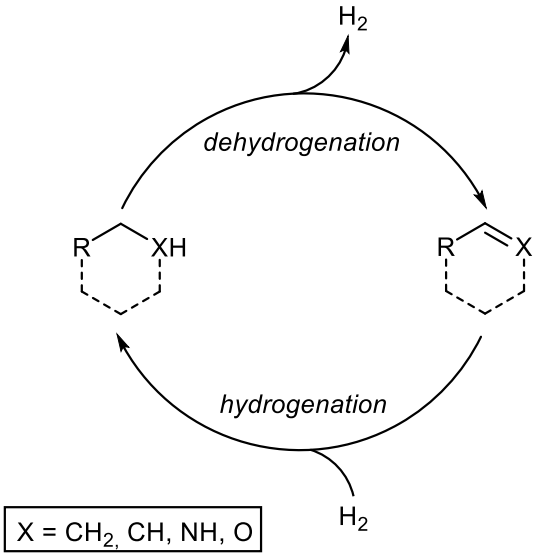


entry	catalyst	oxidant	additive	solvent	T (°C)	t (h)
1[57]	10 % MnO_x/HAP	air	-	toluene	80	24
2[58]	50 mg/mmol Cs/MnO_x	air	-	toluene	110	3
3[59]	1 % Au/HAP	bubbling O_2	-	toluene	60	16
4[60]	0.02 % Au/TiO_2	1 atm O_2	10 % $KOCH_3$	methanol	rt	24
5[72]	10 % $Fe(NO_3)_3$*$9H_2O$	air	10 % TEMPO, 50 % KOH	toluene	80	36
6[70]	5 % Ag/Al_2O_3	air	-	toluene	100	24
7[71]	0.1 % Ag(NHC)	dry air	110 % $BnMe_3NOH$	toluene	rt	12
8[64]	0.3 % Pt-Sn/γ-Al_2O_3	0.1 MPa O_2	-	ethylbenzene	138	24
9[69]	5 % $(HQ)_2V(O)(OiPr)$	0.1 MPa O_2	-	dichloromethane	80	20
10[63]	1 % Pd/ZrO_2	air	10 % KOH	alcohol substrate	30	6
11[62]	1 % $Pd(OAc)_2$	air	4 % TEMPO, 15 % Et_3N, 20 % *t*BuOK	neat	rt	72
12[61]	2 % Pd(AlO(OH))	1 atm O_2	-	heptane	90	20
13[65]	5 % Cu_2O	1 atm O_2	150 % KOH	toluene	70	19
14[66]	1 % Cu_2(bpnp)(μ-OH)$(HCOO)_3$	1 atm O_2	50 % $CsOH*H_2O$	neat	110	16
15[68]	1 % CuI	air	2 % TEMPO, 1 % bipy	acetonitrile	rt	12
16[67]	1 % $Cu(OAc)_2$	air	1 % TEMPO, 2 % DMAP	neat	110	24

Moreover, simple bases such as NaOH (10 mol%)[73] and KOH (stoichiometric)[74] have been shown to catalyze the oxidative coupling of amines and alcohols in the presence of air at 90-100 ºC. Furthermore, coupling of primary amines can be achieved by refluxing the amines in water under one atmosphere of oxygen pressure, the so-called "on-water" reaction.[75]

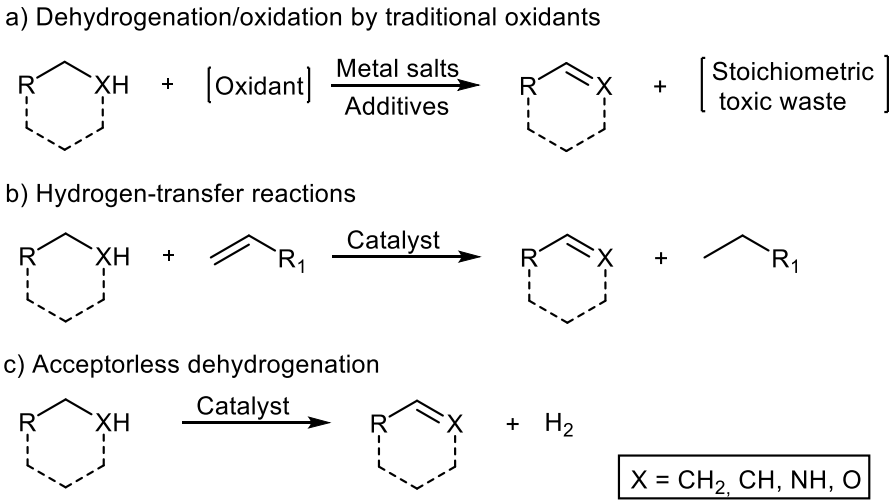
3.3 Acceptorless dehydrogenation (AD) of primary alcohols

Even the use of environmentally friendly oxidants such as air and O_2 cannot avoid the possibility of over-oxidation of the substrates, leading to various possible by-products. In addition, pressurized oxygen pose explosion hazards. Hence, another solution is desired. In organic chemistry, a large number of reactions involve catalytic transfer of hydrogen. The hydrogen can be either abstracted (dehydrogenation) or added (hydrogenation) to the organic compound in the form of molecular hydrogen or as a hydride and a proton, leading to the formation of the corresponding oxidized or reduced product, respectively (Scheme **3.4**). In the case of dehydrogenation, the removal of hydrogen from an organic compound is in the majority of cases a thermodynamically unfavorable process. Hence, the biggest problem of this transformation is to push the equilibrium towards the products.



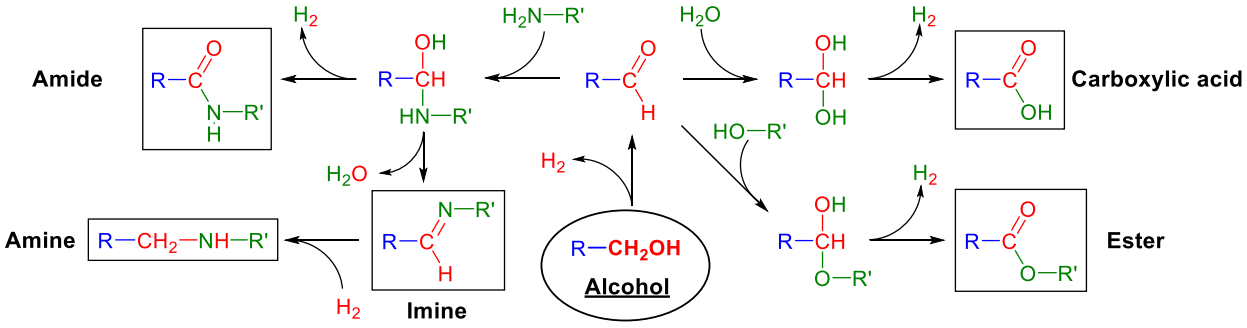
Scheme 3.4. Catalytic dehydrogenation vs. hydrogenation

As mentioned previously, the traditional methods to oxidize organic compounds such as alcohols involve the transfer of hydrogen atoms from the substrate to an oxidant, the so-called acceptor, or a sacrificial hydrogen acceptor molecule, e.g. an olefin. In both cases, extensive amounts of waste is produced. An efficient and environmentally benign alternative to this process is acceptorless dehydrogenation (AD), in which a catalyst removes hydrogen atoms, which then leave the reaction on their own in the form of H_2 gas with no need of a stoichiometric oxidant or a sacrificial acceptor molecule (Scheme **3.5**).[76] In general, dehydrogenations convert less reactive substrates (e.g. alcohols, alkanes and amines) into more reactive substrates (e.g. aldehydes, alkenes and imines) in an efficient and non-polluting way. These intermediates resulting from the initial dehydrogenation can then undergo a variety of successive transformations creating new C-C and C-N bonds, leading to a range of useful products, providing an assortment of applications in organic synthesis, in addition to the formation of valuable hydrogen gas. These steps proceed under 'one-pot' conditions with a single catalyst, usually a transition metal complex, and only hydrogen gas and, in the case of condensations reactions, water are formed as by-products.[77] Hydrogenation and dehydrogenation represent the microscopic reverse of each other, and therefore many catalysts are able to perform both dehydrogenations and hydrogenations.



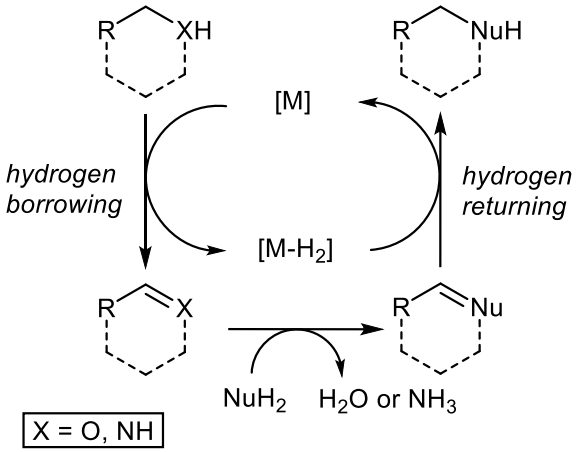
Scheme 3.5. Classes of dehydrogenation/oxidation reactions: a) traditional method to oxidize organic compounds leading to a stoichiometric amount of toxic waste, b) hydrogen-transfer reactions – the liberated hydrogen binds to a sacrificial acceptor molecule, c) acceptorless dehydrogenation – the liberated hydrogen gas is removed from the reaction mixture.

If we more specifically look at the dehydrogenation of primary alcohols, also known as acceptorless alcohol dehydrogenation (AAD), this process produces the corresponding aldehydes, which can then be converted into esters, carboxylic acids, imines, amines and amides in the same pot (Scheme **3.6**).[76,78]



Scheme 3.6. Pathways for dehydrogenative reactions from primary alcohols.

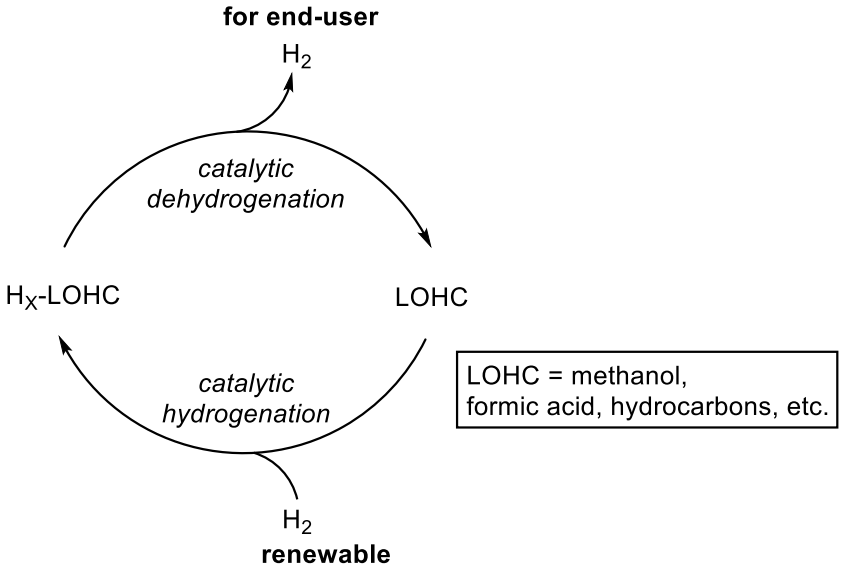
After the removal of the hydrogen, two things can happen with this sole by-product. Either the liberated H_2 gas is removed from the reaction mixture to help switching the equilibrium towards the products and collected for potential use elsewhere or the generated hydrogen is returned *in situ* to the unsaturated molecule after it has undergone a further transformation (e.g. a condensation reaction). The latter is known as the so-called "borrowing-hydrogen" (BH) process (Scheme **3.7**).[76] In the BH approach, the atom economy is even higher than for the pure AD reaction, since more atoms from the starting material are incorporated into the final product. Additionally, the use of molecular hydrogen is avoided.[77]



Scheme 3.7. Catalytic borrowing-hydrogen process.

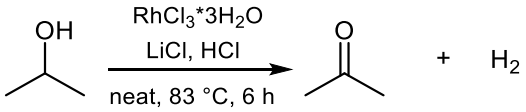
The evolved hydrogen gas is valuable in itself as a clean, high-energy fuel, which is of significant importance with today's environmental concerns and anticipation of fossil fuel depletion, since hydrogen is considered one of the future alternatives to traditional fossil fuels. Unfortunately, hydrogen is highly flammable and storage as well as transportation is both difficult, expensive and dangerous. When AD is performed reversibly on small substrates such as methanol and formic acid, the released hydrogen is considered to be the target product of the transformation. These substrates act as hydrogen carriers that produce pure H_2 with CO_2 being the only by-product. Such gas feed can be directly utilized for fuel applications in the concept of "liquid organic hydrogen carriers" (LOHC) (Scheme **3.8**), solving part of the problem of storage and transportation.[79]

In general, AAD and related dehydrogenative coupling reactions have the potential for redirecting synthetic strategies (including the synthesis of imines) toward green chemistry with the use of sustainable resources (principle 7) and catalysts (principle 9), thereby avoiding toxic reagents (principle 3) and undesirable side reactions, leading to high atom economy (principle 2), with no waste generation (principle 1) (Figure **2.1**).



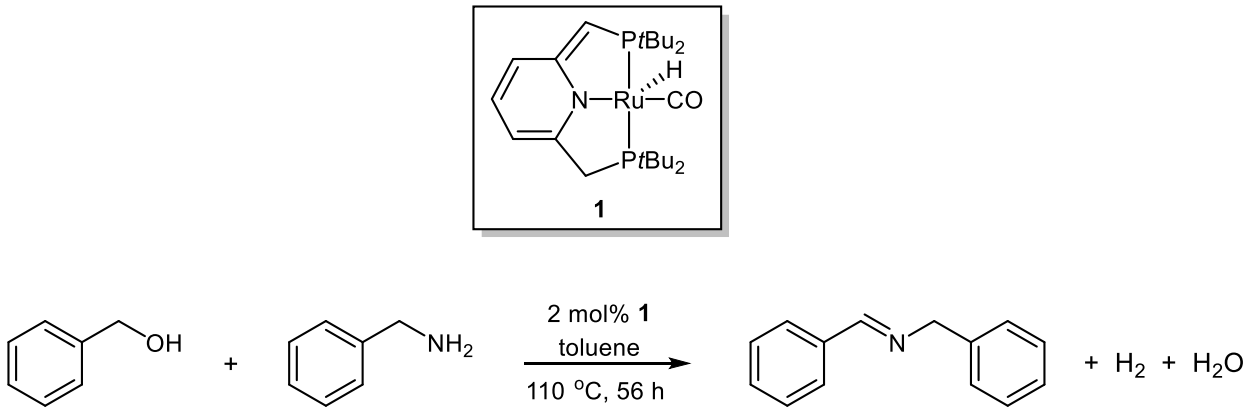
Scheme 3.8. Schematic representation of the LOHC concept.

One of the important inventors of AAD reactions was Marcel Guerbet, who in 1899 reported that the dehydrogenation of linear primary alcohols lead to the formation of β-branched primary alcohols due to a condensation of the intermediate aldehydes followed by dehydration and hydrogenation without the use of conventional oxidants, long before hydrogen-transfer reactions were reported.[80] One of the very first examples of AAD was reported in 1967, when Charman showed that rhodium(III) chloride was capable of dehydrogenating isopropanol to acetone without a hydrogen acceptor (Scheme **3.9**).[81]



Scheme 3.9. Early example of AAD reaction; dehydrogenation of isopropanol employing rhodium chloride.

Since then several examples of AAD using different catalysts have been published and in 2010, Milstein reported the first dehydrogenative coupling of an amine and an alcohol to the corresponding imine using a ruthenium complex as the catalyst (Scheme **3.10**).[82]



Scheme 3.10. First example of dehydrogenative coupling of a primary alcohol and an amine.

The dehydrogenative transformations are usually catalyzed by homogeneous catalysts from the platinum group metals with palladium, ruthenium, rhodium and iridium as the preferred noble metals.[77,78,83–89] However, these are all precious metals. The price of these metals is very high (Figure **3.1**) and additionally subjected to price fluctuations, since 80% of the annual production comes from just two countries, South Africa and Russia. This makes them economically unpredictable. Furthermore, a low global production of less than 25 tons/year and high toxicity for living organisms give some limitations. The latter is especially an issue, if the catalytic transformations are being used in the production of pharmaceuticals. If the removal of the toxic metal residues from the final product is difficult, the purification costs can increase drastically.[83]

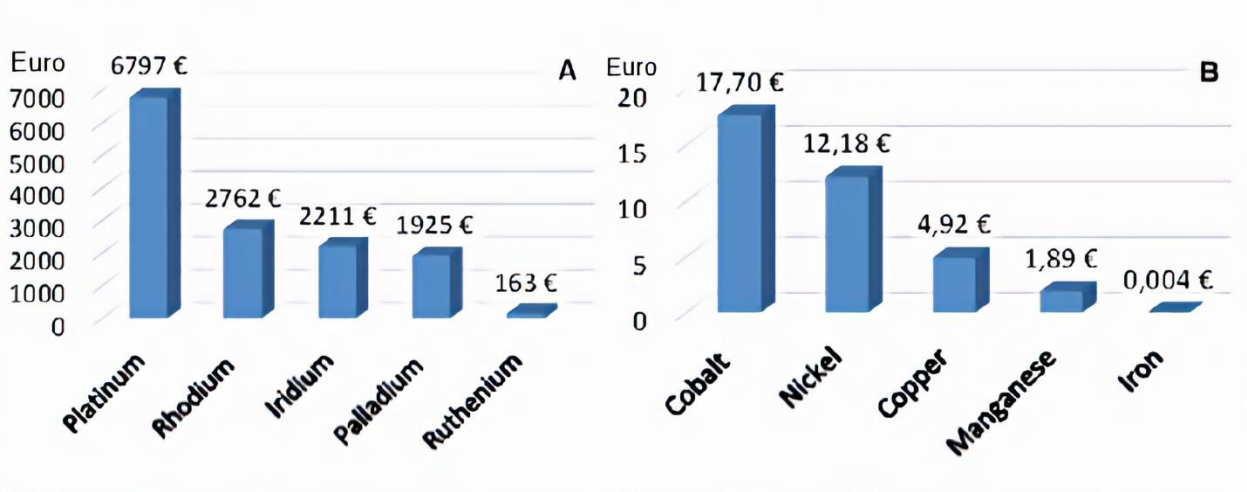
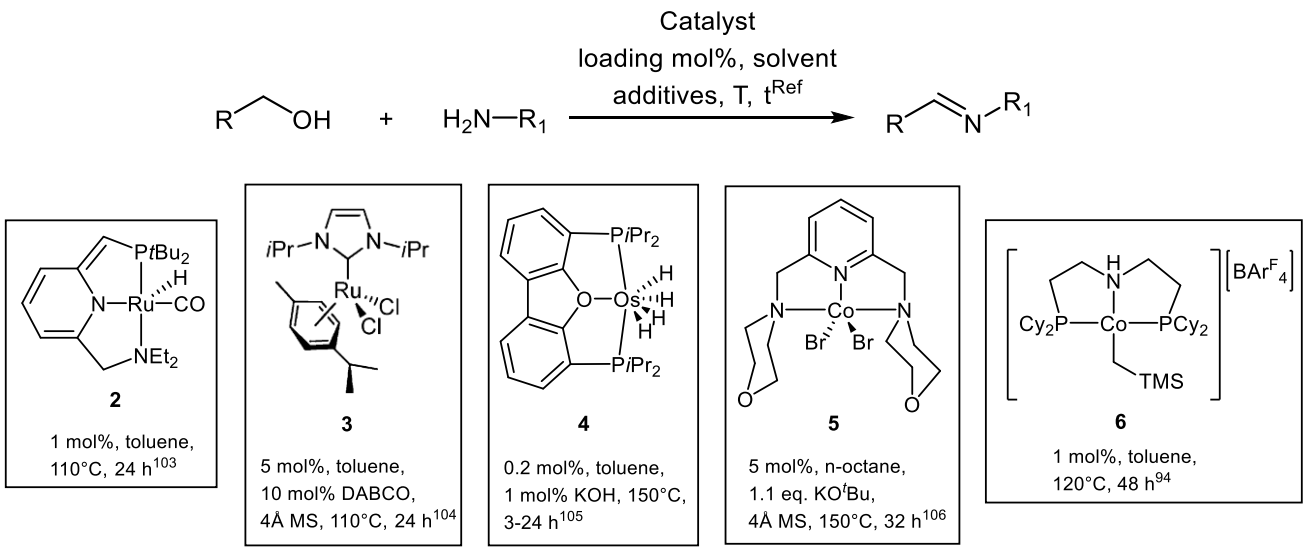


Figure 3.1. Comparison of prices for selected noble metals (A) vs. selected Earth-abundant metals (B).[90]

As a result, in term of environmental sustainability and safety, avoiding the use of noble metals for these transformations is highly desirable and the development of new non-noble metal catalysts with similar catalytic properties, which are both abundant and less- or non-toxic, became a hot topic in the field of catalysis in the last decade. This has led to the discovery of non-noble 3d transition-metal complexes in particular based on iron, cobalt and manganese with the ability to catalyze alcohol dehydrogenations.[83,91–93,] The first AAD cobalt and iron complexes were introduced in 2013 by Hanson[94] and Beller,[95] respectively (possibly Singh[96] actually reported the first iron complex, but he never called it a dehydrogenation and he did not look for hydrogen), whereas the first AAD manganese complex was introduced by Milstein in 2016.[14] Also examples with copper,[97–100] zinc[101] and molybdenum[102] have been described. Some examples of different transition metal catalysts used for AAD imine synthesis are shown in Scheme **3.11**.[94,103–106]

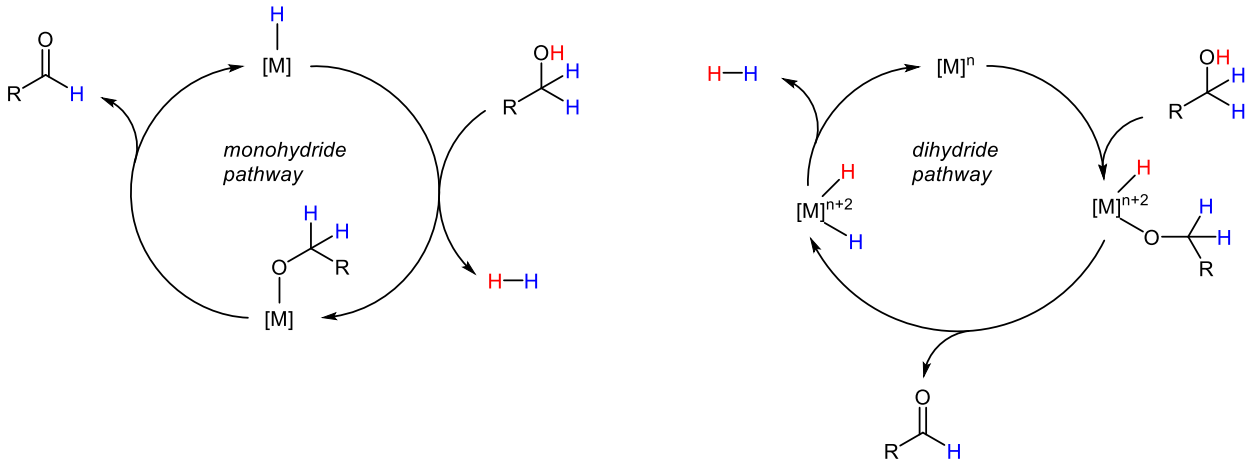


Scheme 3.11. Transition metal complexes for AD coupling of primary alcohols and amines to give imines.

3.4 The classical AAD reaction mechanism

Many of the early examples of AAD reactions have turned out to be operating through a Shrock-Osborn inner-sphere reaction mechanism,[107] which is now divided into a "monohydride" and a "dihydride" version[108–110] (Scheme **3.12**). The two reaction mechanisms differ in various aspects, but the most obvious difference is that in case of the "dihydride" mechanism, two hydrogens are

transferred to the metal center (the O-*H* and Cα-*H* from the alcohol substrate), whereas the metal only receives one hydride in the "monohydride" mechanism (the Cα-*H* from the alcohol substrate). Consequently, in case of reversibility, scrambling between the two different hydrogens will be observed in the "dihydride" mechanism, whereas scrambling between the two hydrogens will not occur in the "monohydride" mechanism. This makes it possible to distinguish between the two pathways with the use of deuterium-labelled substrates. Another difference in the two mechanisms is that the oxidation state of the metal is changing during the "dihydride" cycle, whereas the oxidation state of the metal remains the same in the "monohydride" pathway.

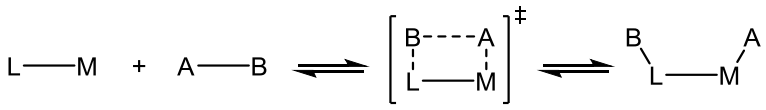


Scheme 3.12. Representation of monohydride pathway (on the left) and dihydride pathway (on the right).

3.5 Metal-ligand cooperation (MLC)

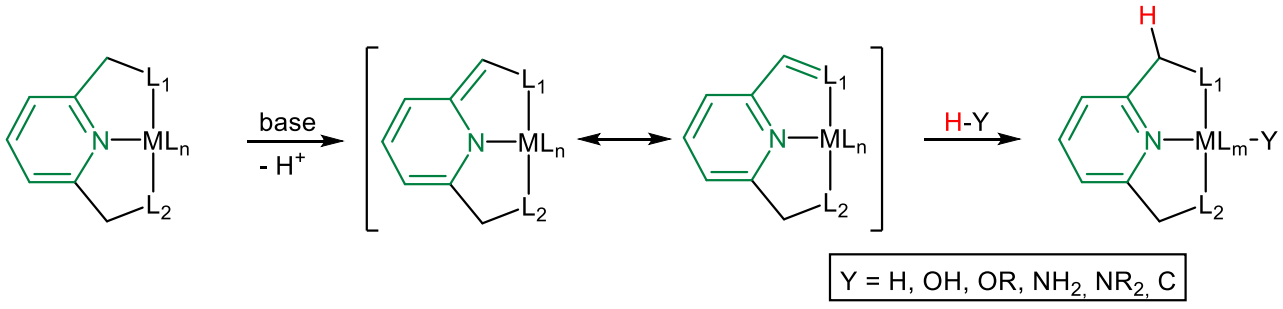
In newer examples of AAD reactions, a new concept of catalysis has turned up, where the role of the ligands have changed. In contrast to "classical" transition metal catalysis, where all key transformations take place at the metal center, while the ligand acts as a simple spectator, MLC, also referred to as a bifunctional pathway, suggests that both the metal and the ligand participates in bond activation processes. In many examples in homogeneous catalysis, oxidative addition, reductive elimination and β-hydride elimination occur at the metal center, while the ligand stays unaltered throughout the reaction as shown above. Nevertheless, in many enzymes bond activation takes place differently and involves an adapted ligand environment that cooperates directly with

the metal in bond activation, resulting in chemical modifications of both the metal center and the ligand (Scheme **3.13**).



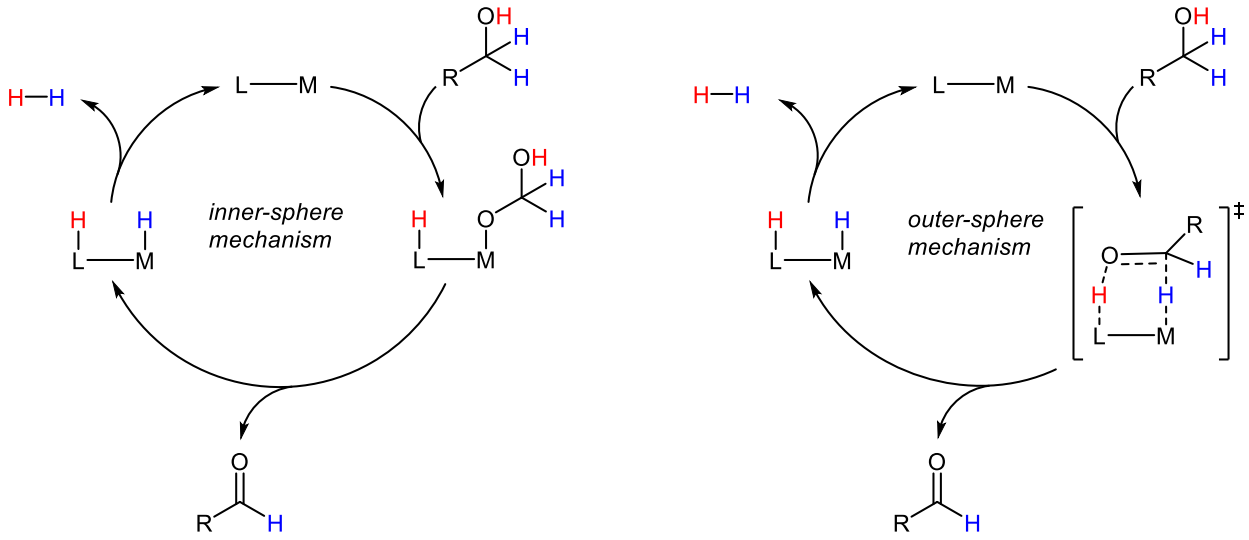
Scheme 3.13. Bond activation by metal-ligand cooperation.

The bifunctional pathway is possible for catalysts possessing a metal center as a Lewis acid and a cooperative site in the ligand as a Brønsted base, enabling acid-base functionality. The most common MLC systems are based on N-donor ligands, but also other donor atoms such as carbon, oxygen, sulfur and boron have demonstrated a great potential for MLC reactivity. The classical mechanism proceeds through direct participation of the ligand in the catalytic reaction by a reversible proton transfer through cleavage/formation of one of its X-H bonds and the formation of a metal-hydride complex. H-H and H-heteroatom bond activation is among the most well studied and widely used in catalysis. Bifunctional catalysts can be classified as α, β or γ-functionalized, depending on the location of the cooperative site in the ligand framework with respect to the metal center. Furthermore, MLC can be divided into two classes, metal-ligand cooperation through M-L bonds and metal-ligand cooperation through aromatization/dearomatization (Scheme **3.14**).[111,112]



Scheme 3.14. Metal-ligand cooperation through aromatization-dearomatization.

The transfer of the proton and the hydride can happen either by a stepwise inner-sphere reaction mechanism or by a concerted outer-sphere reaction mechanism (Scheme **3.15**). As the name implies, the transfer of the proton to the ligand and the hydride to the metal is concerted in the outer-sphere mechanism. In contrast, in the case of the inner-sphere mechanism, abstraction of the proton by the ligand leads to the formation of a metal alkoxide intermediate, which is subsequently converted to the metal hydride during the β-hydride elimination. Hence, the transfer of the proton and the hydride is stepwise.

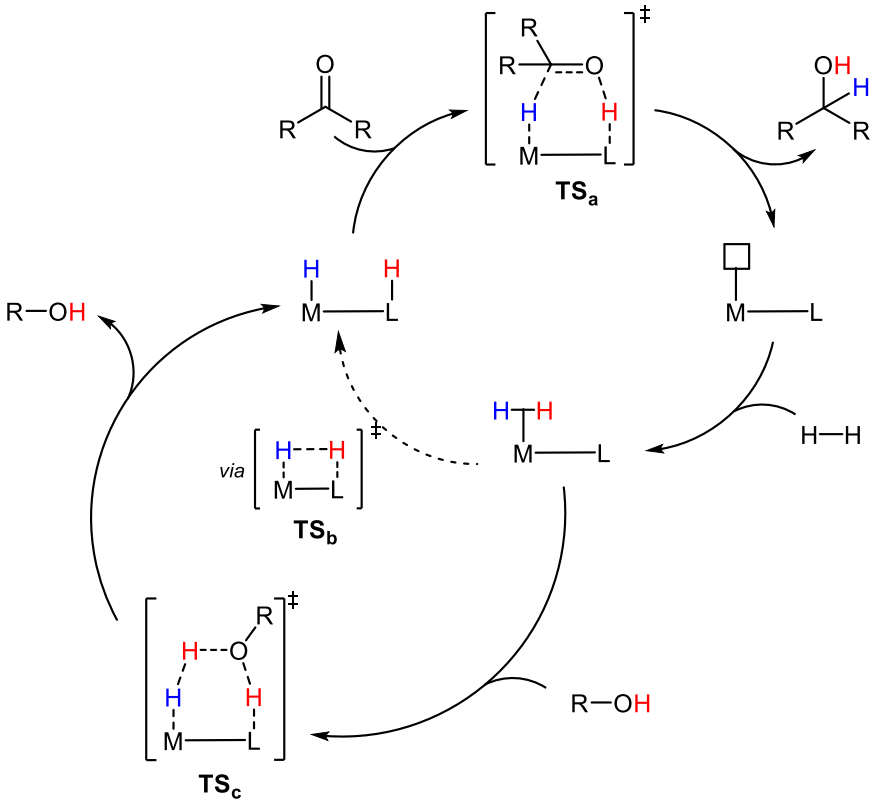


Scheme 3.15. Representation of inner-sphere (on the left) and outer-sphere (on the right) mechanism in bifunctional pathways.

Cooperative action of a reactive heteroatom center at a ligand and a metal center may offer a suitable acid-base bifunctionality and spatial arrangement for selective bond activation processes under mild conditions, resembling bond activation reactions that occur in enzymes.[111]

The first "chemically non-innocent" ligand was reported by Shvo in 1985.[113] About ten years later, Noyori published an outer-sphere bifunctional mechanism for the hydrogenation of ketones (Scheme **3.16**), which today is the most commonly accepted bifunctional mechanism.[114–116] Since

then, that particular mechanism has been revised[114] and many other examples of complexes capable of MLC have been published,[111,114,117] both AD systems and new hydrogenation reactions.



Scheme 3.16. Noyori mechanism for the hydrogenation of ketones.

In conclusion, AAD must be considered a green alternative to traditional methods to synthesize various functional groups, including imines. Moving towards the use of catalysts based on Earth-abundant metals will make AAD even more valuable. In the development of new catalysts, it is worth to keep in mind the advantages of complexes capable of MLC.

4. Development and mechanistic investigation of manganese(III) salen-catalyzed dehydrogenation of alcohols

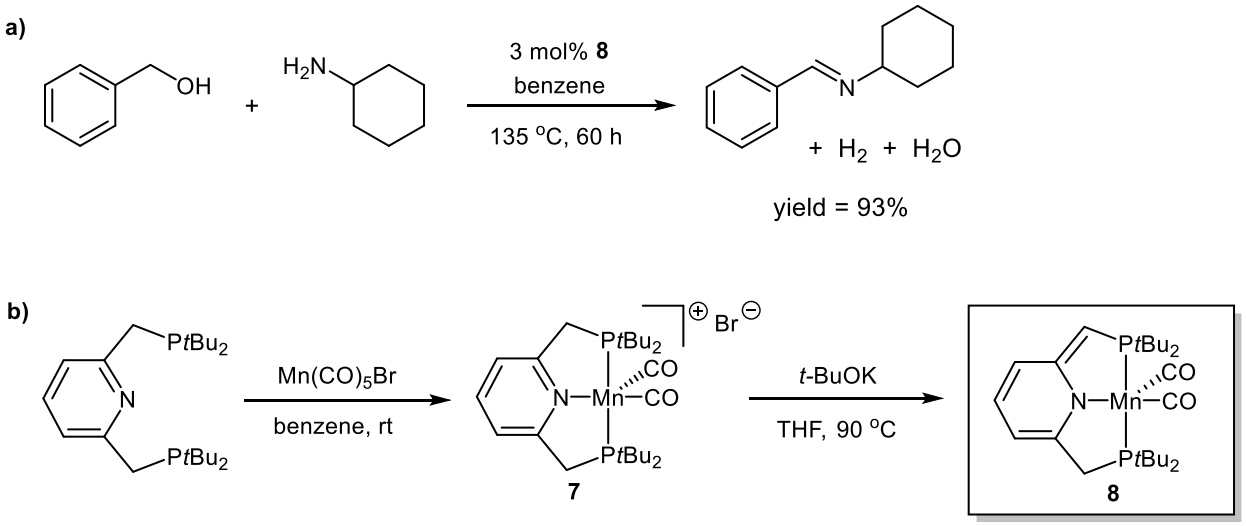
This chapter is based in part on the following article:

Samuelsen, S. V.; Santilli, C.; Ahlquist, M. S. G.; Madsen, R. Development and mechanistic investigation of the managense(III) salen-catalyzed dehydrogenation of alcohols. *Chem Sci*., **2019**, *10*, 1150-1157.[118] - Published by the Royal Society of Chemistry.

4.1 Background

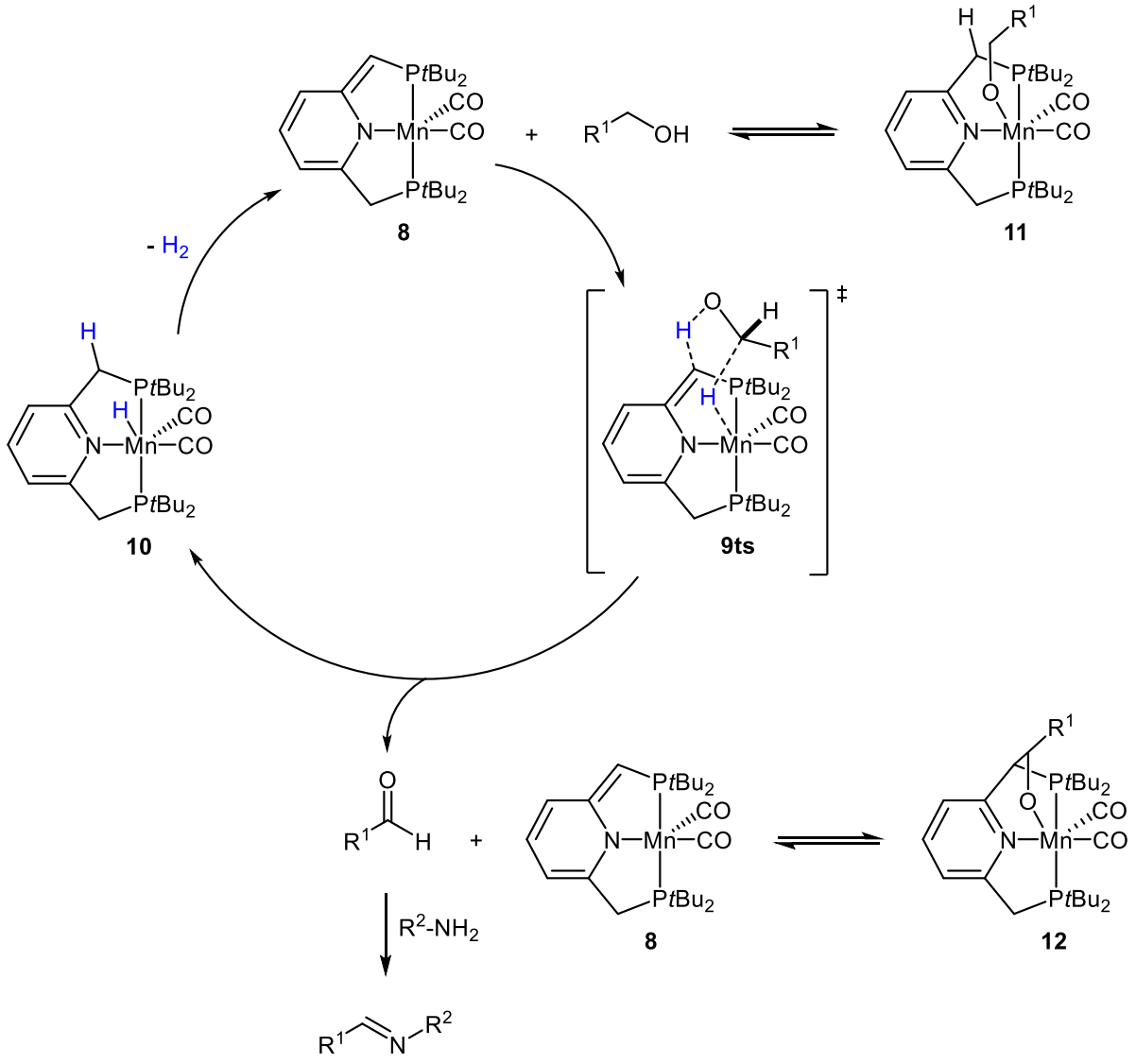
4.1.1 Manganese-catalyzed AD reactions

Manganese is the third most abundant transition metal of the Earth's crust (surpassed only by iron and titanium). It is an exceptional element that is capable of existing in eight oxidation states, providing its salts and coordination compounds with versatile reactivity in organic reactions.[119] Furthermore, as seen in Figure **3.1** it is less expensive as well as less toxic than the noble metals and is therefore a potentially useful noble metal "replacement".[92] Additionally, manganese is present in a variety of metalloenzymes in humans. These enzymes play a vital role in metabolism, antioxidant systems and development.[93] Previously, manganese compounds have been used in a variety of reactions,[119,120] but preferentially in oxidation and coupling reactions, owing to manganese's high redox potential and its coordination state.[121] As previously mentioned, the reactivity of manganese complexes in dehydrogenation reactions was demonstrated for the first time in 2016 by Milstein and coworkers, where a 2,6-bis(di-*tert*-butylphosphinomethyl)pyridine (PNP) pincer manganese complex was able to catalyze the dehydrogenative cross-coupling of alcohols with amines to form imines. The reaction occurred with 3% manganese complex at 135 ºC in dry benzene over 60 h (Scheme **4.1a**).[14] The manganese complex is prepared from $Mn(CO)_5Br$ and the belonging pincer ligand resulting in a cationic complex **7**, which is subsequently treated with *t*-BuOK to form the actual catalyst **8** (Scheme **4.1b**).[14]



Scheme 4.1. a) Dehydrogenative synthesis of imines catalyzed by complex **8**, b) synthesis of manganese PNP pincer complex **8**.

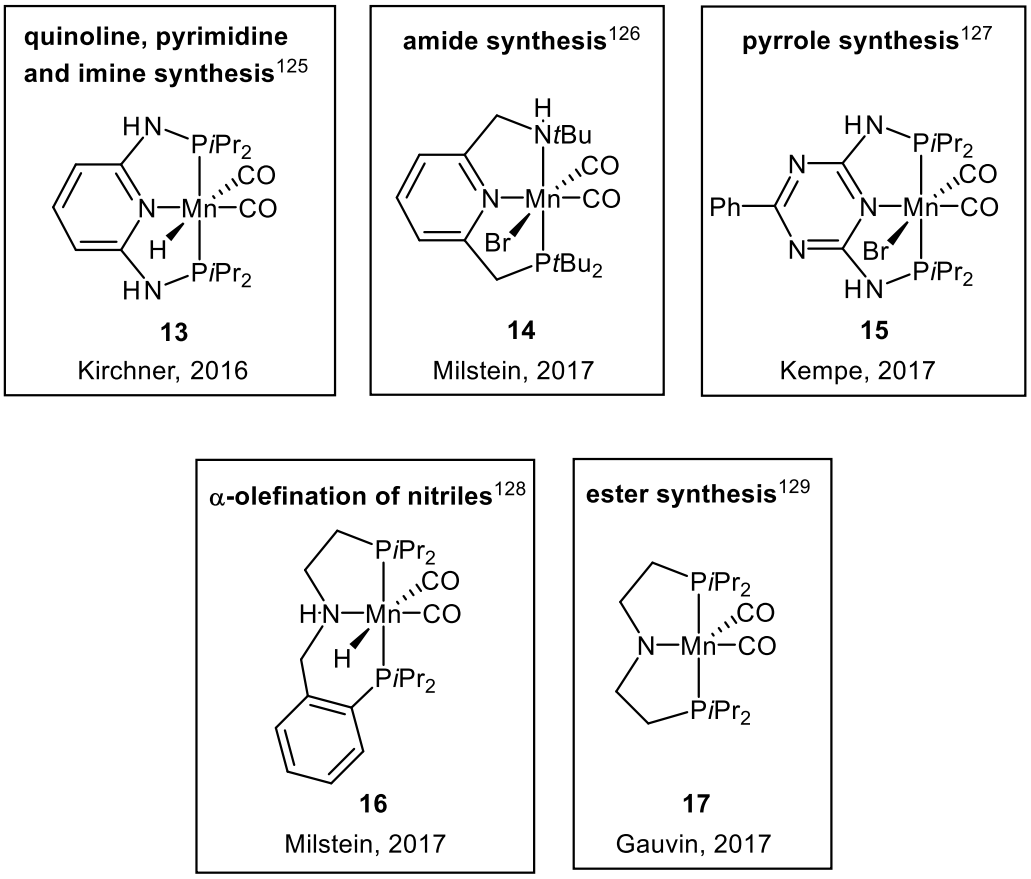
MLC through dearomatization and aromatization of the pincer ligand plays a key role in the proposed mechanism for the dehydrogenative synthesis of imines with catalyst **8** (Scheme **4.2**). The dehydrogenation of the primary alcohol proceeds through a concerted, bifunctional proton and hydride transfer to the ligand and metal, respectively (**9ts**). Hereafter, the newly formed aldehyde is released, which reacts with the amine to form the imine product. Meanwhile, the active catalyst **8** is restored by dihydrogen liberation from complex **10**. At the same time, the primary alcohol can coordinate to catalyst **8** to afford the alkoxo manganese complex **11**. Furthermore, the formed aldehyde can perform an electrophilic attack on the dearomatized ligand, leading to complex **12**. Neither complex **11** nor **12** is a part of the actual catalytic cycle.[14]



Scheme 4.2. Proposed dehydrogenative MLC mechanism for imine formation catalyzed by complex **8**.

Since then several different manganese complexes have been used in dehydrogenative coupling reactions for preparing various other functional groups and heterocyclic frameworks such as cyclic imides,[122] formamides,[123] pyrimidines,[124,125] amides,[126] pyrroles,[127] quinolines,[125] α-olefination of nitriles[128] and esters[129] (Scheme **4.3**). In all cases, the reactions are running at temperatures between 80-140 ºC in 18-72 h with a catalyst loading of 0.5-5 mol%. In some cases, 10-200 mol% of a base is used as an additive. Different manganese complexes have also been used to catalyze

the *N*-alkylation of amines[130,131] and ketones[132] through the "borrowing-hydrogen" process as well as hydrogenation of carbonyl groups,[133,134,135] amides,[136] esters[137,138] and nitriles.[135]



Scheme 4.3. Manganese(I) complexes for different alcohol dehydrogenation reactions.

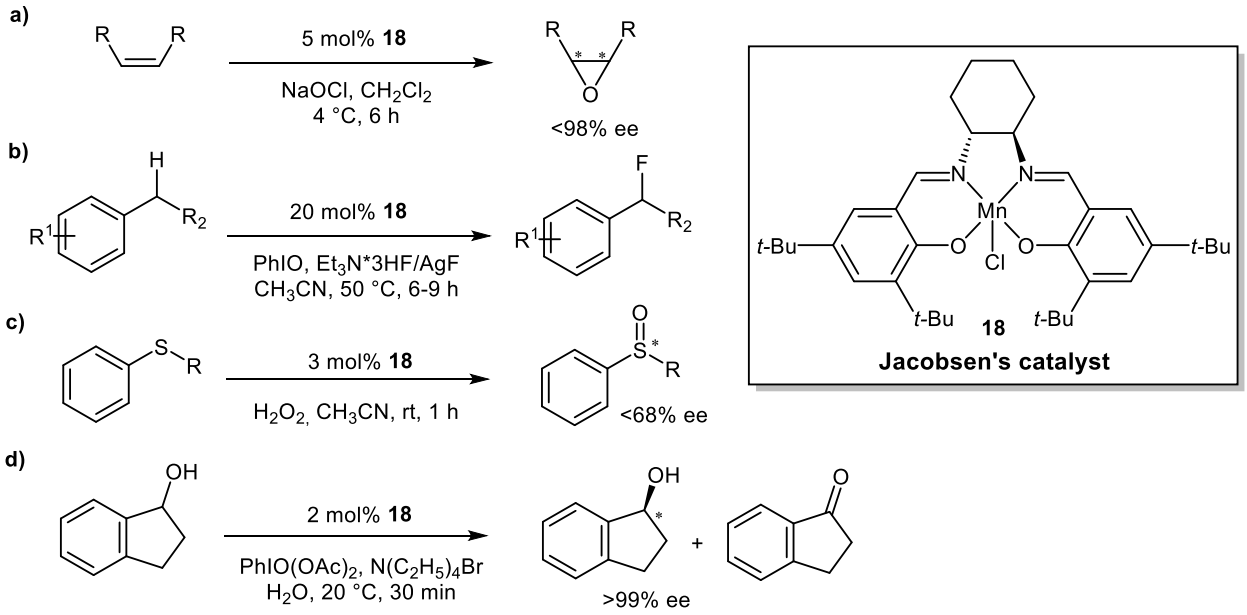
Notably, the previously developed complexes are all manganese(I) compounds with CO ligands and a tridentate pincer ligand. The mechanism for the dehydrogenation with all these complexes is believed to involve a catalytic cycle with different manganese(I) species,[123,137,139] as was the case with Milsteins manganese catalyst **8**. Additionally, no catalytic activity is observed without the CO ligands or with the corresponding manganese(II) dihalide complexes.[118,133] Most commonly the pincer ligands are nitrogen-centered and comprise strongly donating phosphine ligands as sidearms. The popularity of pincer ligands, which have also been used together with ruthenium, iridium, palladium, iron, cobalt, nickel and molybdenum,[121] is often explained by the combination

of the high metal binding strength and their ability to engage into MLC behavior. Therefore, it should also be mentioned that the majority of the described applications of manganese-based pincer complexes are not only depending on the metal-center itself, but more likely on the cooperative action of the nitrogen atom and the metal center in close proximity.[121] The +I oxidation state of manganese has so far appeared to be an inflexible requirement for the catalytic activity, which give rise to considerable synthetic limitations. The preparation of manganese(I) complexes faces a major drawback that is related to a very limited selection of manganese(I) precursors, e.g. $Mn_2(CO)_{10}$ and $Mn(CO)_5Br$. Both of these carbonyl complexes are quite expensive due to the difficult preparation by a carbonylation reaction.[140,141] Also the otherwise very popular phosphorus-containing pincer ligands are a cost-determining factor.[121] Furthermore, the electron-withdrawing CO ligand is necessary for stabilization of the low oxidation state of manganese,[118] and they are also usually difficult to replace, which confines the potential profusion of reactions available for manganese complexes.[83] Hence, although manganese is an Earth-abundant and cheap metal, the manganese(I) complexes from Scheme **4.3** are not inexpensive. Furthermore, they have to be handled in a glovebox due to stability problems. As a result, there was a need for identifying a new, easy to synthesize and more abundantly available class of manganese complexes for alcohol dehydrogenations, which does not rely on the use of ligands with strong phosphine donors, but instead efficient and cheap ligands based on C, H, N, O elements.[83] Especially, it would be attractive to catalyze the dehydrogenations by higher valent manganese complexes, where stabilization by CO ligands is not necessary[118] and where work outside a glovebox is possible.

4.1.2 Motivation for this project and previous work with manganese(III) complexes

Synthesis of various complexes of manganese bearing polyamine, phthalocyanine, porphyrin, pincer or salen ligands have been reported.[93] The applicability of a catalytic method is closely related to the availability of the catalyst and can be seriously undermined if the preparation of the catalyst turns out too costly or difficult.[142] M(salen) complexes can be readily prepared from a diamine, a salicylaldehyde derivative and a metal ion. Various chiral and achiral salicylaldehydes, diamines and metal ions are commercially available or are easily synthesized. Hence, a variety of M(salen) complexes can be prepared with ease.[143] Salen-type ligands have been complexed with several different metals such as chromium,[144] ruthenium, titanium, zinc,[145] cobalt, iron[146] and

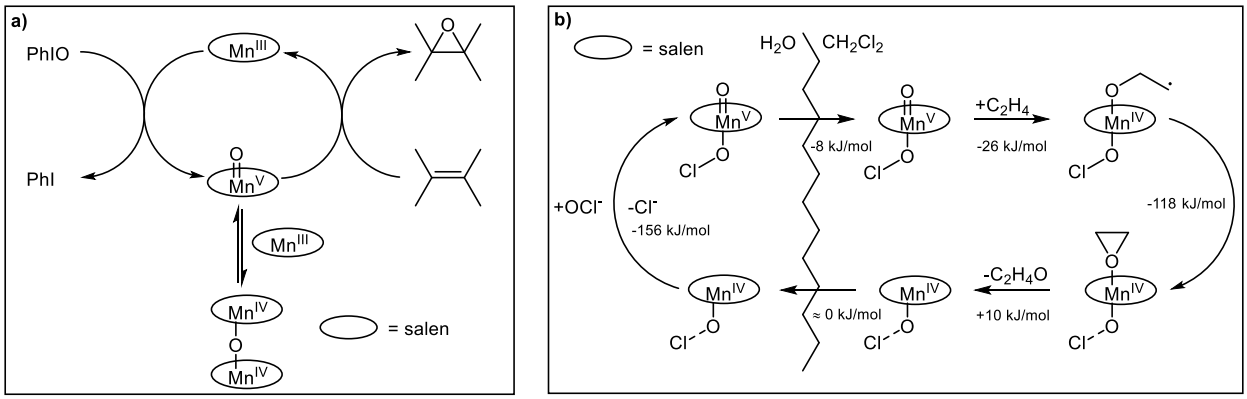
manganese[143] to be used as catalysts in a variety of reactions, including epoxidation of olefins, hydroxylation and halogenation of alkanes, oxidation of alcohols, formation of C-N bonds, oxidation of sulfides, oxidation of enol derivatives, kinetic resolution of racemic alkenes and allenes, benzylic oxidation, desymmetrization of meso- and prochiral substrates, sulfimidation, cyclopropanation and the Baeyer-Villiger reaction, all in presence of a stoichiometric oxidant.[119,120,143] In 1991, Eric Jacobsen announced an optimized system for the catalytic asymmetric epoxidation of unfunctionalized alkenes using a manganese(III) salen complex, which was later named Jacobsen's catalyst.[147] Since then this complex has been used in more of the above-mentioned reactions (Scheme **4.4**).



Scheme 4.4. Structure of Jacobsen's catalyst and a selection of reactions in which it has been used as catalyst. a) epoxidation of olefins,[147] b) benzylic C-H fluorination,[120] c) oxidation of sulfides,[148] d) kinetic resolution of secondary alcohols.[149]

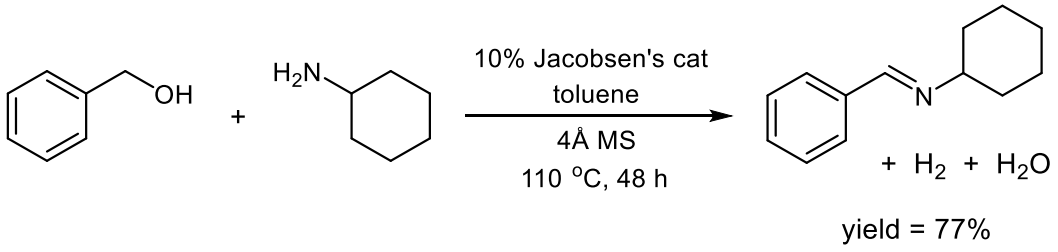
The originally published mechanism for the Mn(III) salen-catalyzed epoxidation of alkenes by Kochi and co-workers is shown in Scheme **4.5a**. Here, the reaction is believed to proceed through a catalytic cycle with different manganese(III), (IV) and (V) species.[150] In the years, many investigations have been made about this mechanism. One of the newest suggested mechanisms

was reported by Cavallo and H. Jacobsen, who suggested that the active species has a hypochlorite ligand *trans* to the oxo group and that manganese does not return to Mn(III) (Figure **4.5b**).[151]



Scheme 4.5. a) Catalytic cycle for the epoxidation of alkenes proposed by Kochi and co-workers, b) catalytic cycle proposed by Cavallo and H. Jacobsen.

When looking for a more stable, higher valent, easy to synthesize catalyst, Jacobsen's catalyst seemed to be a good choice as catalyst for acceptorless dehydrogenation of alcohols. While actually screening for a more convenient *in situ*-formed catalyst system, previous PhD student Carola Santilli discovered that the easily available Jacobsen's catalyst indeed could liberate hydrogen gas from benzyl alcohol and the transformation was applied to the synthesis of an imine from benzyl alcohol and cyclohexylamine (Scheme **4.6**).

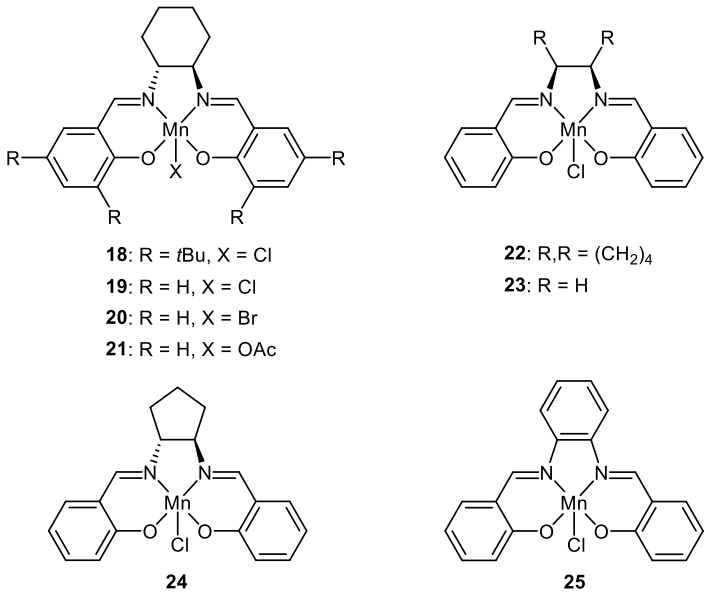


Scheme 4.6. Dehydrogenative imine synthesis catalyzed by Jacobsen's catalyst.

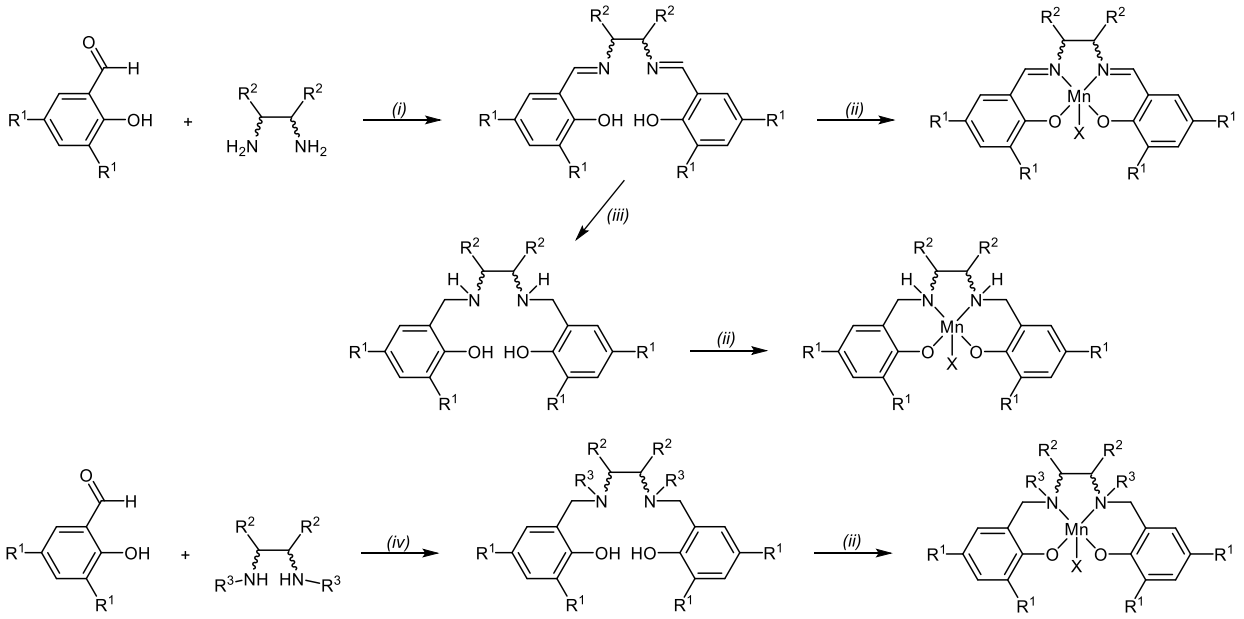
4.2 Results and discussion

4.2.1 Catalyst design and optimization of the reaction conditions

After this discovery, the author of this thesis took over the project. First, several derivatives of Jacobsen's catalyst were prepared to investigate the influence of the aryl substituent, the axial ligand on manganese, the scaffold and the Schiff base functionality on the catalyst activity[118] (Scheme **4.7**). As mentioned previously, the complexes are easily synthesized. The salen ligands were prepared by simple condensation between a salicylaldehyde derivative and a diamine, whereas the salan ligands where either synthesized by reductive amination or by reducing the imines of the corresponding salen ligand. The complexes were prepared simply by mixing the ligand and a manganese(II) source with the desired axial substituent under aerobic conditions (Scheme **4.8**). All the complexes are highly stable and can be stored at room temperature for more than 1 year without affecting the activity. It should be mentioned that Jacobsen's catalyst **18** is commercially available, but the best and most consistent results were obtained when the catalyst was synthesized by standard protocols. In fact, Jacobsen's catalyst purchased from Sigma Aldrich failed to perform the imination reaction while the complex acquired from Strem Chemicals catalyzed the transformation successfully. Therefore, only in house synthesized complexes were employed in this chapter, where no issues with reproducibility were observed.



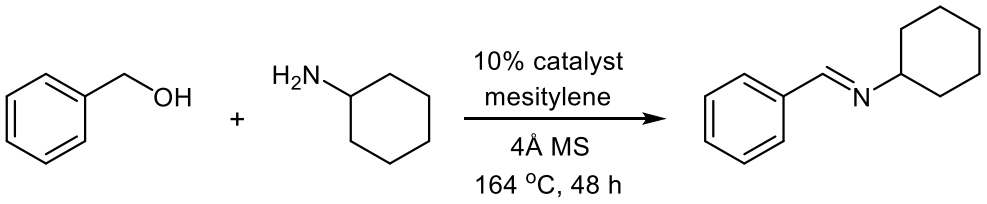
Scheme 4.7. Manganese(III) complexes used for dehydrogenative imine synthesis.



Scheme 4.8. Synthesis of various derivatives of Jacobsen's catalyst. *Reagents and conditions: (i)* EtOH, reflux, 4 h. *(ii)* MnX_2, air, EtOH, reflux, 2 h. *(iii)* $NaBH_4$, MeOH, reflux, 1 h. *(iv)* $NaCNBH_3$, acetic acid, rt, 72 h.

The synthesized complexes were investigated as catalysts for the dehydrogenative coupling of benzyl alcohol and cyclohexylamine using 10 mol% of the catalyst in refluxing mesitylene under a flow of N_2 (Table **4.1**). 4Å molecular sieves (MS) were added as additive to push the equilibrium in the direction of the imine. Essentially the same result as with Jacobsen's catalyst (entry 1) was obtained with the unsubstituted analogue **19** (entry 2) and the *tert*-butyl groups can therefore be omitted. The axial substituent on manganese, on the other hand, needs to be chloride, since both bromide (**20**) and the acetate (**21**) gave significantly lower conversion and yield (entries 3 and 4). The same was observed when the *trans*-1,2-diaminocyclohexane scaffold was changed to either the *cis* (**22**), the ethylene (**23**), the cyclopentane (**24**) and the benzene (**25**) analogue (entries 5-8).[118] In the end, complex **19** was selected as catalyst for the dehydrogenative transformation.

Table 4.1. Acceptorless alcohol dehydrogenation with manganese(III) salen/salan complexes.



entry[a]	catalyst	BnOH conversion (%)[b]	imine yield (%)[b]
1	**18** (Jacobsen's catalyst)	81	79
2	**19**	86	81
3	**20**	70	65
4	**21**	66	64
5	**22**	83	74[c]
6	**23**	60	58
7	**24**	28	27
8	**25**	27	25

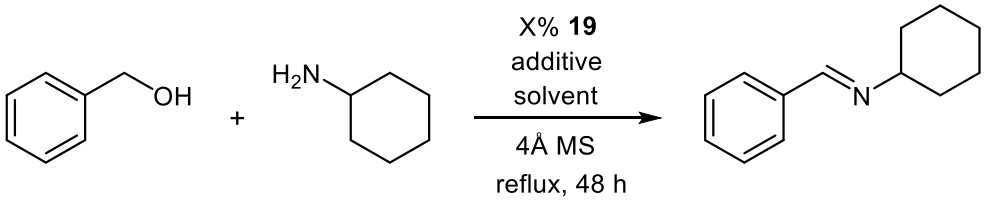
[a]Conditions: BnOH (1 mmol), $CyNH_2$ (1 mmol), catalyst (0.1 mmol), 4Å MS (150 mg), mesitylene (4 mL), reflux, 48 h. [b]Determined by GC-MS with tetradecane as internal standard. [c]6% of *N*-cyclohexylbenzamide was also formed.

For further optimization, the influence of additives and solvent were investigated (Table **4.2**). A number of common additives were included in the reaction, but they all led to lower imine yields due to a moderate conversion of benzyl alcohol (entries 1-15). Previously, nitride salts as a basic additive for alcohol dehydrogenations have been used in the Robert Madsen Group,[86] but lower conversion and yields were also observed when Li_3N and Mg_3N_2 were added to the reaction (entries 16 and 17). However, with Ca_3N_2 as an additive a complete transformation of benzyl alcohol and high yield of the imine was observed (entry 19). The optimum amount of Ca_3N_2 was 16.7% since both higher and lower quantities decreased the yield of the imine (entries 18 and 20-22). Interestingly, 16.7% is an intriguing number since one equivalent of Ca_3N_2 can theoretically react as a base with 6 equivalents of either alcohol or water. The influence of the solvent was then investigated and a slightly improved outcome was observed upon conducting the reaction in toluene (entry 28). 1,4-Dioxane, *p*-cymene, diglyme, *o*-xylene and heptane gave lower yields due to incomplete conversion of benzyl alcohol (entries 23-27). The catalyst loading could be adjusted to 5% without affecting the imine yield, while 2.5% and 1.25% gave lower conversion of the alcohol (entries 29-31). A modest amount of imine was formed, when the reaction was conducted

in the absence of complex **19** (entry 32). The role of Ca_3N_2 is probably to act as both a base and desiccant. Replacing Ca_3N_2 with the desiccants $MgSO_4$ or Na_2SO_4 led to slower reaction (entries 33 and 34), while molecular sieves had no influence on the transformation (entry 35). Ca_3N_2 reacts with water to form $Ca(OH)_2$ and NH_3 gas. Interestingly, this salt gave almost the same result as Ca_3N_2 (entry 36). Eventually, 5% of **19** and 16.7% of Ca_3N_2 in refluxing toluene under a flow of N_2 were chosen as the optimum conditions for conversion of equimolar amounts of alcohol and amine.[118]

After the imination reaction has gone to completion and the reaction is cooled to room temperature, it is possible to recover 95% of complex **19** by addition of a small amount of hexane, which makes the catalyst to precipitate. Furthermore, the retrieved complex can be subjected to a new catalytic reaction, which gave 82% yield of the imine with a 4.5% catalyst loading.[118]

Table 4.2. Optimization of acceptorless alcohol dehydrogenation with complex **19.**



entry[a]	X	additive	amt of additive (%)	solvent	BnOH conversion (%)[b]	imine yield (%)[b]
1	10	LiBr	20	mesitylene	24	14
2	10	LiCl	20	mesitylene	32	30
3	10	LiF	20	mesitylene	52	49
4	10	$MgBr_2$	20	mesitylene	69	27[c]
5	10	KOH	20	mesitylene	32	29
6	10	*t*-BuOK	20	mesitylene	54	30[d]
7	10	Et_3N	20	mesitylene	54	49
8	10	$AgBF_4$	20	mesitylene	24	10[e]
9	10	MgO	20	mesitylene	66	59
10	10	Cs_2CO_3	20	mesitylene	70	62
11	10	K_2CO_3	20	mesitylene	70	22
12	10	pyridine	20	mesitylene	70	30
13	10	K_3PO_4	20	mesitylene	41	33
14	10	NaOH	20	mesitylene	52	51
15	10	LiOH	20	mesitylene	65	56

16	10	Li_3N	20	mesitylene	66	12[f]
17	10	Mg_3N_2	20	mesitylene	54	48
18	10	Ca_3N_2	33	mesitylene	100	84
19	10	Ca_3N_2	20	mesitylene	100	92
20	10	Ca_3N_2	16.7	mesitylene	100	93
21	10	Ca_3N_2	10	mesitylene	100	90
22	10	Ca_3N_2	5	mesitylene	100	88
23	10	Ca_3N_2	16.7	*p*-cymene	82	80[g]
24	10	Ca_3N_2	16.7	diglyme	39	14[h]
25	10	Ca_3N_2	16.7	*o*-xylene	60	56
26	10	Ca_3N_2	16.7	1,4-dioxane	65	62
27	10	Ca_3N_2	16.7	heptane	20	18
28	10	Ca_3N_2	16.7	toluene	100	98
29	5	Ca_3N_2	16.7	toluene	100	96
30	2.5	Ca_3N_2	16.7	toluene	76	73
31	1.25	Ca_3N_2	16.7	toluene	69	66
32	-	Ca_3N_2	16.7	toluene	20	18
33[i]	5	$MgSO_4$	20	toluene	80	77
34[i]	5	Na_2SO_4	20	toluene	81	79
35[i]	5	Ca_3N_2	16.7	toluene	100	97
36[i]	5	$Ca(OH)_2$	20	toluene	99	95

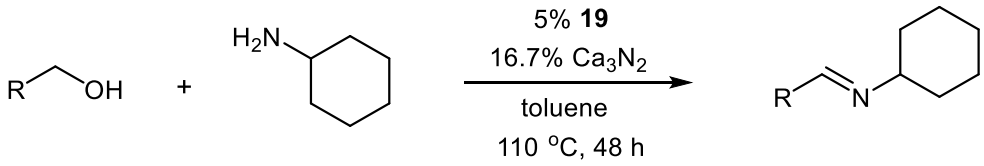
[a]Conditions: BnOH (1 mmol), $CyNH_2$ (1 mmol), **19** (X/100 mmol), additive, 4Å MS (150 mg), solvent (4 mL), reflux, 48 h. [b]Determined by GC with tetradecane as internal standard. [c]37% of *N*-benzylcyclohexanamine was also formed. [d]23% of *N*-benzylcyclohexanamine was also formed. [e]3% of *N*-benzylcyclohexanamine was also formed. [f]6% of *N*-cyclohexylbenzamide was also formed. [g]4% of *N*-benzylcyclohexanamine was also formed. [h]23% of *N*-benzylcyclohexanamine was also formed. [i]Without 4Å MS.

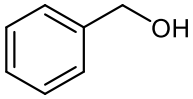
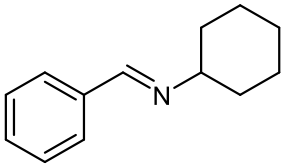
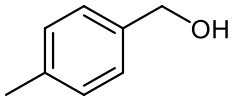
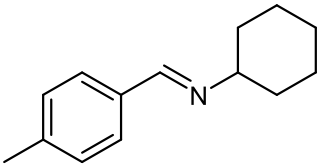
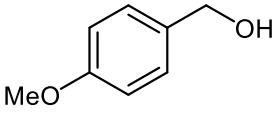
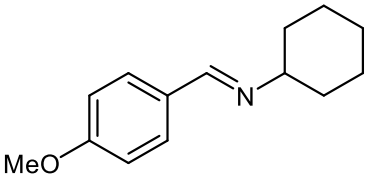
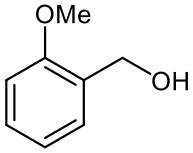
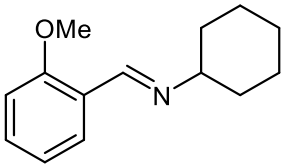
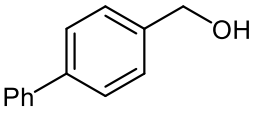
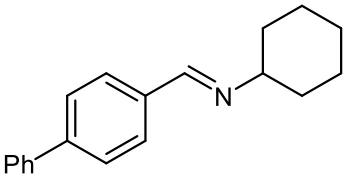
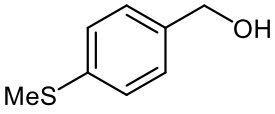
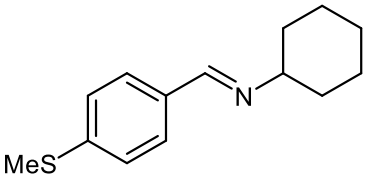
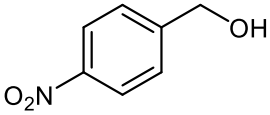
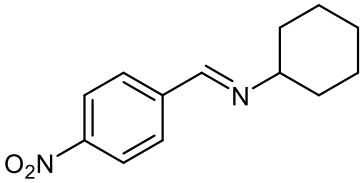
4.2.2 Substrate scope and limitations

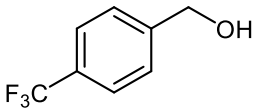
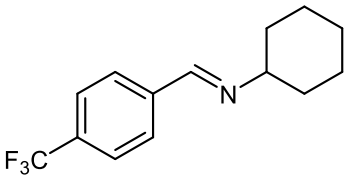
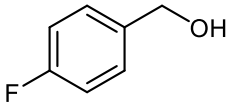
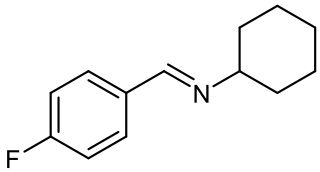
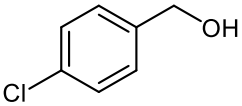
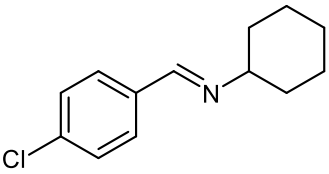
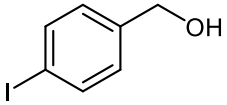
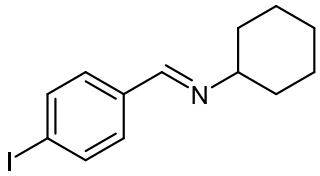
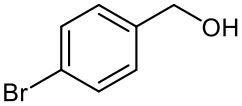
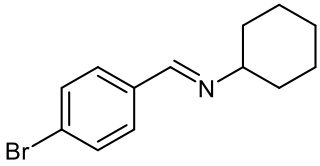
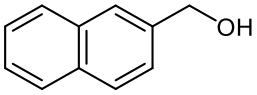
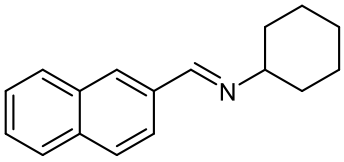
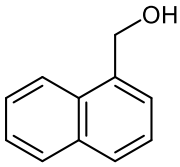
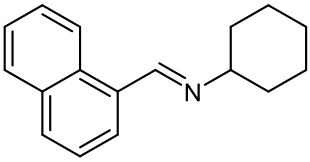
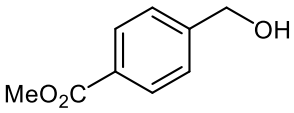
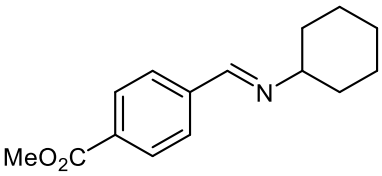
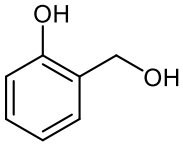
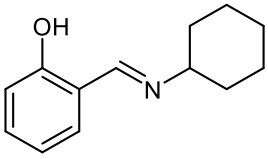
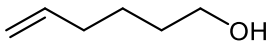
With the optimized catalyst system in place, the substrate scope of the imination reaction could now be investigated. Cyclohexylamine was first reacted with different alcohols and the imines were isolated by flash chromatography (Table **4.3**). This produced 89% for the parent reaction with benzyl alcohol, while the *p*-methyl analogue furnished 70% yield (entries 1 and 2). The *p*- and *o*-methoxy-substituted substrates afforded 83% and 90%, respectively, while *p*-benzyl and *p*-methylthiobenzyl alcohol both gave 60% yield (entries 3-6). *p*-Nitrobenzyl alcohol is often a challenging substrate in dehydrogenative transformations due to an accompanying reduction of the

nitro group,[35,76,77,78,152,153] but this was not observed here and the imine was obtained in 70% yield (entry 7). Likewise, another substrate with a very electron-withdrawing group, the *p*-CF_3 benzyl alcohol, furnished 70% of the imine (entry 8). A *p*-fluoro and a *p*-chloro substituent was also tolerated giving 73% and 85% yield (entries 9 and 10). The analogous *p*-bromo and *p*-iodo substrate reacted slightly slower although no competing dehalogenations were observed (entries 11 and 12). In addition, the two isomeric naphthalenemethanols gave the corresponding imines in 71% and 60% yield (entries 13 and 14). In all the above-mentioned cases of Table **4.3**, full conversion was observed, except for entries 5, 6, 11 and 13, where 5-25% of the alcohol remained and thus accounted for the lower yields in those cases.[118] On the other hand, methyl *p*-(hydroxymethyl)benzoate and *o*-hydroxybenzyl alcohol were challenging substrates, yielding only 26 and 28% of imine, respectively (entries 15 and 16). In both cases, the conversion was relatively high, but unfortunately, the by-products were not characterized. Possible explanations could be that because the phenol group of *o*-hydroxybenzyl alcohol has a $pK_a \approx 10$, this moiety could be deprotonated by Ca_3N_2 during the reaction. This would maybe electronically disfavor the imine synthesis. Therefore, the reaction was tried again both with stoichiometric amounts of base and without base, but unfortunately a better result was not obtained. In case of methyl *p*-(hydroxymethyl)benzoate, this could be hydrolyzed by the base, giving the corresponding acid. Furthermore, both the ester and the possible acid may not be very soluble in toluene, since precipitation was observed in the reaction, both when the reaction was run with and without base. This could explain the assumable high conversion, but small amounts of observable products, since the precipitation will not be detected in GC-MS.

Table 4.3. Imination of alcohols with cyclohexylamine catalyzed by complex **19**.

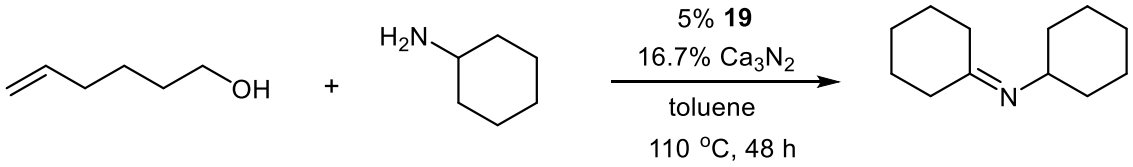


entry[a]	alcohol	imine	alcohol conv. (%)[b]	imine yield (%)[c]
1			100	89
2			100	70
3			100	83
4			100	90
5			90	60
6			95	60
7			100	70

8			95	70
9			100	73
10			100	84
11			100	61
12			75	61
13			100	71
14			94	60
15			83	26
16			87	28
17		-	14	0

[a]Conditions: alcohol (1 mmol), $CyNH_2$ (1 mmol), **19** (0.05 mmol), Ca_3N_2 (0.167 mmol), toluene (4 mL), reflux, 48 h.
[b]Determined by GC-MS with tetradecane as internal standard. [c]Isolated yield.

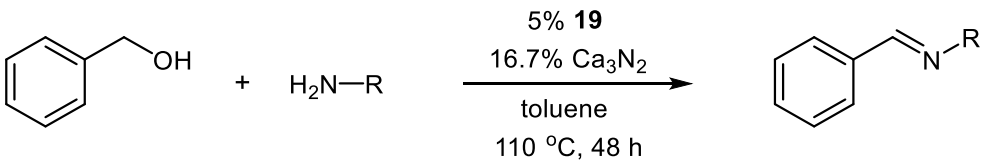
When aliphatic alcohols were tested as substrates, the desired imine was unfortunately not obtained. Instead, dehydrogenation of the amine substrate lead to the dehydrogenative homocoupling of the amines as the only observed product (Scheme **4.9**). The possibility of using complex **19** in amine homocoupling reactions was not investigated further in this PhD study, but it could be an interesting project in the future.

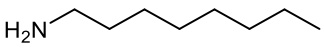
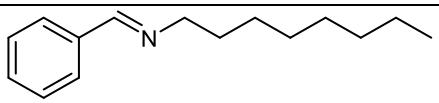
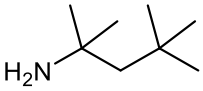
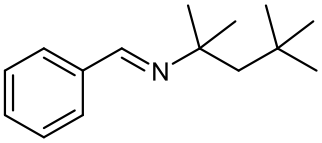
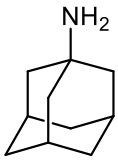
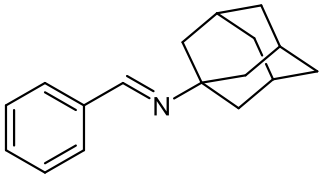
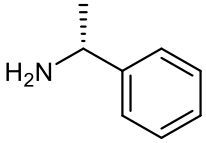
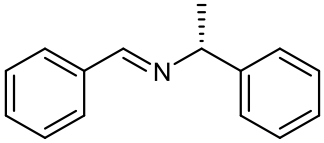
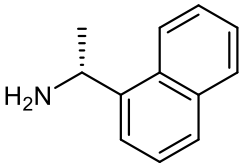
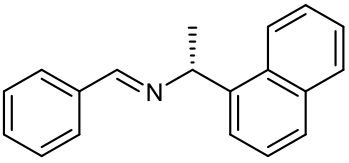
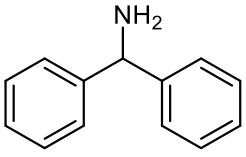
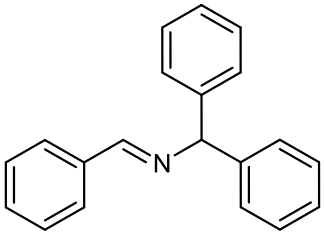
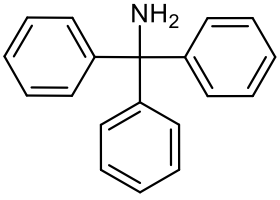
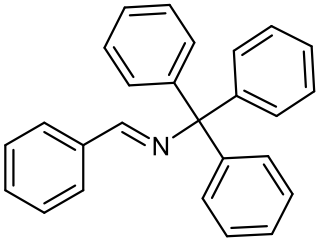


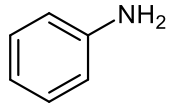
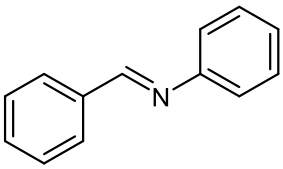
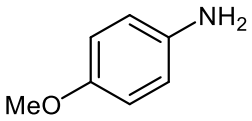
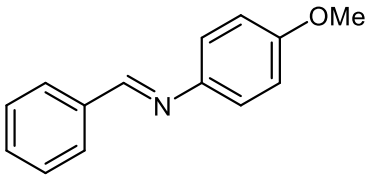
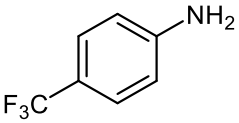
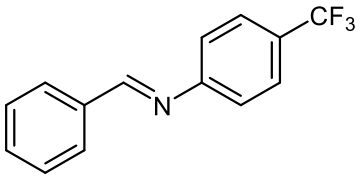
Scheme 4.9. Dehydrogenative homocoupling of amine substrates.

The influence of the amine was then investigated by reacting benzyl alcohol with different primary alcohols (Table **4.4**). Octylamine gave essentially the same result as cyclohexylamine (entry 1). The more hindered amines *tert*-octylamine and 1-adamantylamine also gave full conversion of benzyl alcohol and furnished the imine in 69% and 88% yield, respectively (entries 2 and 3). Similar yields were obtained with the two optically pure amines (*R*)-1-phenylethylamine and (*R*)-1-(naphthyl)ethylamine although 10-15% of benzyl alcohol remained in both cases (entries 4 and 5). No sign of any racemization was observed in the two transformations indicating that dehydrogenation of the amine is not occurring under the reaction conditions. Benzhydrylamine gave the imine in 73% yield, while tritylamine only furnished 19% yield (entries 6 and 7). In the latter case, 48% of the intermediate benzaldehyde was also observed indicating a poor conversion into the imine with the much-hindered amine. Furthermore, the imination could be performed with anilines, where 74%, 63% and 62% yield were obtained with aniline, *p*-anisidine and *p*-trifluoromethylaniline, respectively (entries 8-10).[118]

Table 4.4. Imination of amines with benzyl alcohol catalyzed by complex **19**.

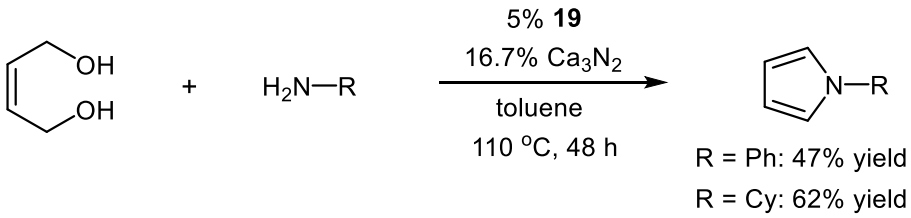


entry[a]	amine	imine	alcohol conv. (%)[b]	imine yield (%)[c]
1			97	91
2			100	69
3			100	88
4			99	66
5			87	83
6			93	73
7			69	17[d]

8			100	74
9			70	63
10			82	62

[a]Conditions: BnOH (1 mmol), amine (1 mmol), **19** (0.05 mmol), Ca_3N_2 (0.167 mmol), toluene (4 mL), reflux, 48 h. [b]Determined by GC-MS with tetradecane as internal standard. [c]Isolated yield. [d]48% benzaldehyde was also observed.

The reaction could be extended to the synthesis of pyrroles by reacting *cis*-but-2-ene-1,4-diol with primary amines. The transformation could be carried out with both aniline and cyclohexylamine to afford the desired product in moderate yield (Scheme **4.10**).[118] This dehydrogenative Paal-Knorr synthesis was first reported by Crabtree in 2011 using a ruthenium complex.[154] Since then, this reaction has also been carried out using other transition metals such as iron[155,156] and palladium.[157] The reaction proceeds through a dehydrogenation of the alcohols leading to the formation of the carbonyl intermediates, which then cyclizes with the elimination of water.

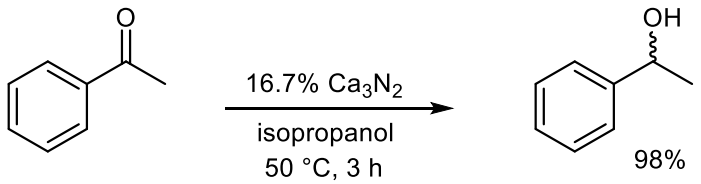


Scheme 4.10. Pyrrole synthesis from but-2-ene-1,4-diol and amines.

Furthermore, it was tried to obtain the corresponding amine of the imine product by closing the system, thereby hoping that the released hydrogen would be returned to the imine. Unfortunately,

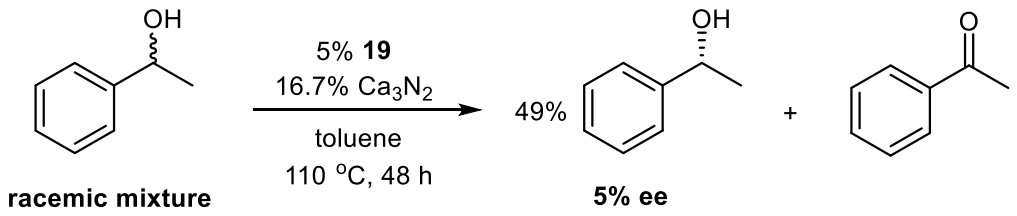
this was not the case. On the other hand, switching the base from Ca_2N_3 to *t*-BuOK, a 56:44 mixture of the imine and corresponding amine was obtained, respectively (this was also shown in Table **4.2,** entry 6). Switching the additive to $MgBr_2$, the amine was actually the major product (37%) (Table **4.2**, entry 4). Additionally, the manganese(III) salen catalyst **19** was studied in several other dehydrogenative reactions, C-H activation and transfer-hydrogenation reactions (appendix **A2**) as well as in hydrogenation reactions (appendix **A1**). Unfortunately, all attempts led to no or poor conversion into the desired products. In all cases, only the corresponding ketones or aldehydes of the alcohol starting materials as well as imine products from either cross-coupling of alcohols and amines or homo- or heterocoupling of amines were observed.

When complex **19** was tested as catalyst in the transfer-hydrogenation of acetophenone using isopropanol as hydrogen source and Ca_2N_3 as base, full conversion of acetophenone into 1-phenylethanol was observed at 50 ºC after 3 hours. Unfortunately, removing complex **19** from the reaction mixture did not affect the outcome. Hence, the reaction was base-catalyzed presumably through a Meerwein-Ponndorf-Verley pathway (Scheme **4.11**).



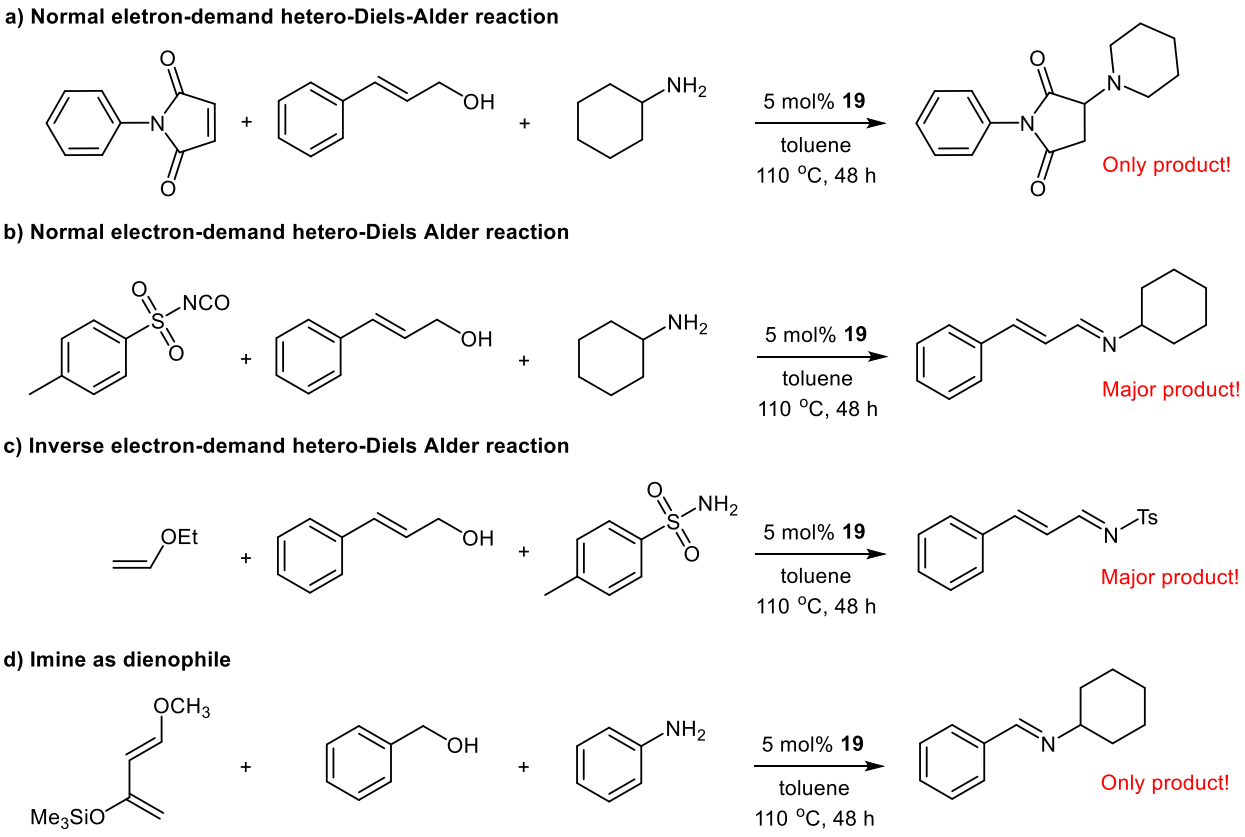
Scheme 4.11. Transfer-hydrogenation of acetophenone catalyzed by Ca_2N_3.

As mentioned in section **4.2**, Jacobsen's catalyst **18** has previously been used in asymmetric reactions, including kinetic resolution of secondary alcohols. Because of this, it was investigated whether complex **19** could as well be used to separate enantiomers in a racemic mixture by dynamic kinetic resolution. An experiment was carried out with 1-phenylethanol and complex **19** in refluxing toluene. After approximately 50% conversion of the alcohol into the corresponding ketone (a minor amount of the aldol product was also observed), the reaction was stopped and the remaining alcohol was isolated and analyzed. Unfortunately, the isolated alcohol was still almost an entirely racemic mixture, since the (*R*)-1-phenylethanol was obtained in only 5% ee (Scheme **4.12**).



Scheme 4.12. Attempted dynamic kinetic resolution of 1-phenylethanol. The reaction was stopped at 50% conversion of the alcohol.

From the results, it seems, only imines can be prepared successfully with complex **20**, but this raises the question, whether it is then possible to use these imines in other reactions? An idea was that if complex **19** could catalyze the coupling of allylic alcohols and amines into the corresponding α,β-unsaturated imines, subsequently, these azadienes could participate in a Diels-Alder reaction (first described by Otto Diels and Kurt Adler in 1928)[158] giving rise to a dehydrogenative Diels-Alder reaction. An experiment was carried out with an allylic alcohol, an amine, *N*-phenylmaleimide as dienophile and complex **19** as Lewis acid catalyst in refluxing toluene. Unfortunately, only the Michael addition product was obtained (Scheme **4.13a**). A dienophile that is not a Michael acceptor was needed. Based on previously published hetero-Diels-Alder reactions using imines as dienes, *p*-toluenesulfonyl isocyanate was chosen as dienophile.[159] However, this time only the α,β-unsaturated imine was observed (Scheme **4.13b**). Both of the two tested approaches are based on Diels-Alder reactions with normal electron-demand. An alternative is the inverse electron-demand Diels-Alder reaction. In this way, the azadiene could be activated by the introduction of a tosyl-group, but again only the imine was obtained, when a dienophile bearing an electron-donating group was added to the reaction (Scheme **4.13c**). A last attempt to develop a dehydrogenative hetero-Diels-Alder reaction was to use the imine as the dienophile instead of as the diene. In 2002, Ding and co-workers reported a three-component one-pot catalyst-free aza-Diels-Alder reaction of Danishefsky's diene with imines.[160] The same reaction was tried with complex **19**, the only difference being that benzaldehyde was exchanged with benzyl alcohol and the solvent was changed from methanol to toluene. Nevertheless, the desired product was not obtained (Scheme **4.13d**).



Scheme 4.13. Attempted hetero-Diels-Alder reactions, a)+b) normal electron-demand and imine as diene, c) inverse electron-demand and imine as diene, d) imine as dienophile.

4.2.3 Investigation of the reaction mechanism

The coupling of primary alcohols with amines to produces imines presented in this chapter is believed to proceed through a dehydrogenation of the alcohol to the aldehyde, which can then react with the amine, and possibly via a MLC pathway. To clarify the mechanism further, several experiments were carried out.

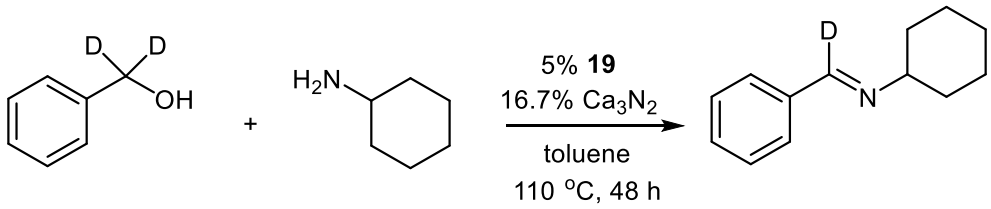
Hydrogen development

To prove that the imine synthesis goes through acceptorless dehydrogenation of benzyl alcohol into benzaldehyde, the gas evolution was measured. This was done by conducting a separate experiment in which benzyl alcohol was reacted with cyclohexylamine, in a Schlenk tube connected to a burette filled with water, under the optimized conditions, except Ca_3N_2 was not

added. Ca_3N_2 was not added to the reaction mixture, since it will produce NH_3 gas under reaction with water, which will be formed during the condensation between benzaldehyde and cyclohexylamine. After 48 hours, 78% of the imine was formed as determined by GC-MS and a total gas volume of 18 mL was collected, which corresponds to one equivalent according to the ideal gas law. The collected gas was identified as dihydrogen by ^{1}H-NMR, which confirms the acceptorless dehydrogenative pathway.

Hammett study and kinetic isotope effect (KIE)

When the optimized reaction (Table **4.2**, entry 35) was performed with α,α-d_2-benzyl alcohol instead of benzyl alcohol, the product was exclusively PhCD=NCy with no hydrogen incorporation into the benzylic position (Scheme **4.14**). This may imply that the dehydrogenation takes place by a monohydride pathway and no metal-dihydride species is formed.[118]



Scheme 4.14. Imination with benzyl alcohol α,α-d_2

To investigate whether the hydride abstraction takes place in the rate-determining step (RDS), the primary kinetic isotope effect (KIE) was measured.[118] To determine the KIE, two separate experiments were set up: one with α,α-d_2-benzyl alcohol and one with benzyl alcohol. By monitoring the reactions by GC-MS, the formation of the two imine products could be followed in time. Assuming that no by-products are formed, the initial rate for both alcohols in the reaction with cyclohexylamine can be determined as the slope of the line, when the concentration of the imine product is plotted against time. Dividing the obtained slopes for the two reactions gave a KIE of 2.3 (Figure **4.1**). This somewhat modest value shows that the non-deuterated alcohol reacts 2 times faster than the deuterated alcohol. This result may imply that breakage of the C-H bond is one of several slow steps in the transformation, which could imply a stepwise mechanism.[118]

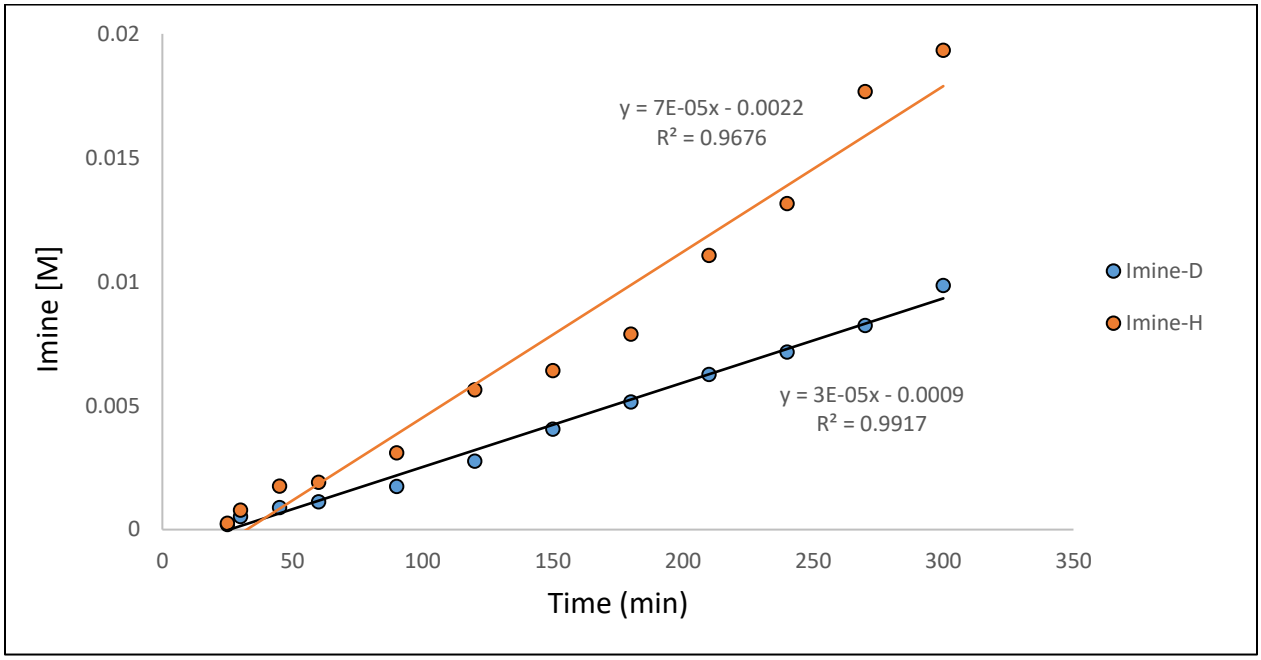
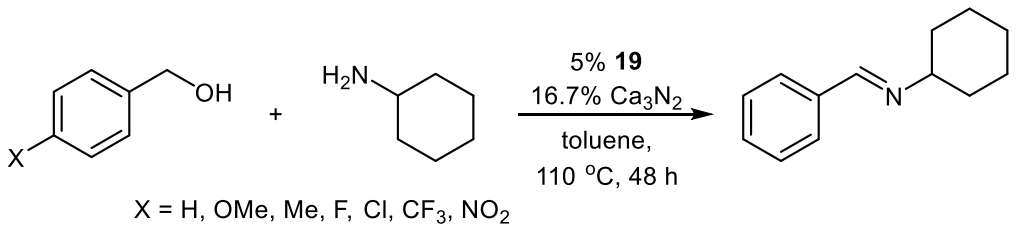


Figure 4.1. Determination of KIE by plotting the initial rates of the reactions involving benzyl alcohol and α,α-d_2-benzyl alcohol.

To gain more experimental information about the reaction pathway, the studies were also supplemented by a Hammett study. Thus, at first five *para*-substituted benzyl alcohols (X = OCH_3, CH_3, F, Cl, CF_3 and NO_2) were allowed to compete with the parent benzyl alcohol in the imination of cyclohexylamine (Scheme **4.15**). The reactions were monitored by GC-MS, which allowed for determining the consumption of each alcohol. Straight lines for all five *para*-substituted benzyl alcohols was obtained by plotting $\ln(c_0/c)$ for one *para*-substituted benzyl alcohol against the same values for benzyl alcohol (Table **4.5**). Their relative reactivities (k_X/k_H) could be determined as the slope of the line, which made it possible to construct a Hammett plot. A good correlation was obtained with the standard σ values[161] giving a straight line with a ρ value of -1.24 (Figure **4.2**). This negative slope shows that substrates with electron-donating groups react faster and that a partial positive charge is built up at the benzylic carbon in RDS consistent with a hydride transfer from the alcohol.[118]



Scheme 4.15. Imination of cyclohexylamine with *para*-substituted benzyl alcohols as part of the Hammett study.

Table 4.5. Overview of Hammett study with *para*-substituted benzyl alcohols.

entry	X	σ	k_X/k_H	$\log(k_X/k_H)$	R^2
1	OMe	-0.27	1.80	0.26	0.984
2	Me	-0.17	1.17	0.07	0.999
3	F	0.06	0.77	-0.11	0.999
4	Cl	0.23	0.38	-0.42	0.998
~~5~~	~~CF_3~~	~~0.54~~	~~1.64~~	~~0.21~~	~~0.994~~
6	NO_2	0.78	0.09	-1.03	0.985

Unfortunately, when *p*-trifluoromethyl benzyl alcohol was allowed to compete with the parent benzyl alcohol in the imination of cyclohexylamine, a point outside the original line was obtained (Figure **4.2,** marked with red circle). This suggests that another mechanism is in play in the case of *p*-trifluoromethyl benzyl alcohol as substrate. However, since this was only one point, it was decided to maintain the Hammett plot obtained from the five original substrates.

Attempts to use different sets of $\sigma^{\bullet}$ values[162–164] gave a poor correlation and radical intermediates are therefore not involved in the catalytic cycle. This was also confirmed by conducting the imination in the presence of one equivalent of the radical trapping agents cyclo-1,4-hexadiene[165] and 2,4-diphenyl-4-methylpent-1-ene,[166] which in both cases had no influence on the imine yield.[118] Furthermore, the two scavengers were not converted during the reactions according to GC-MS analysis.

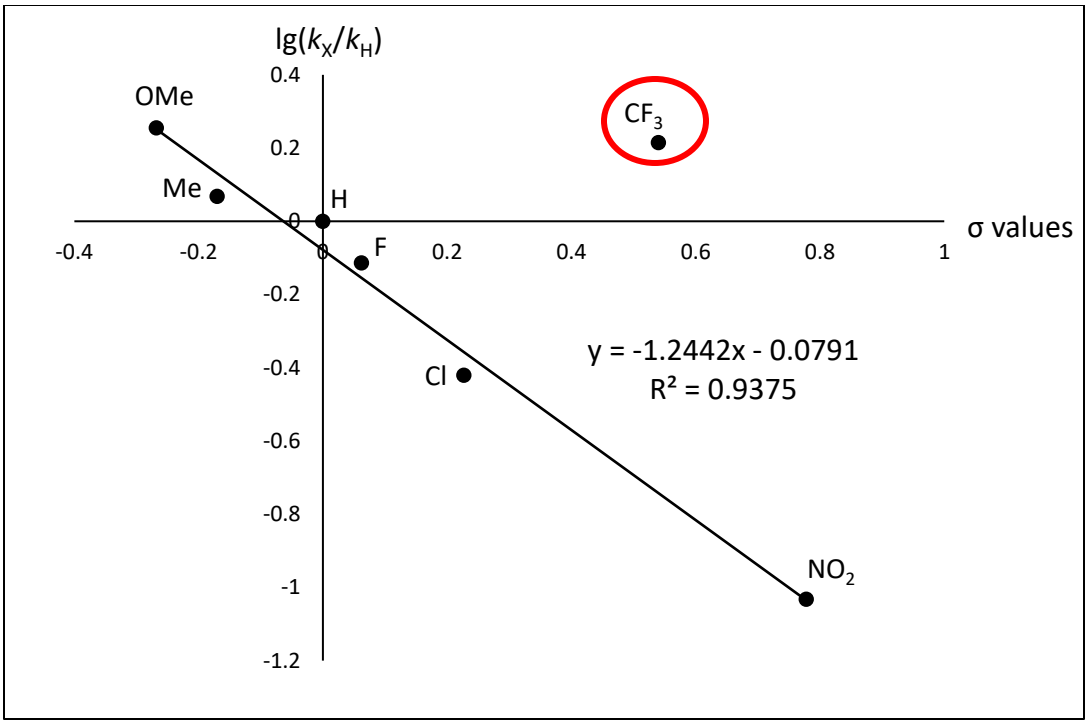
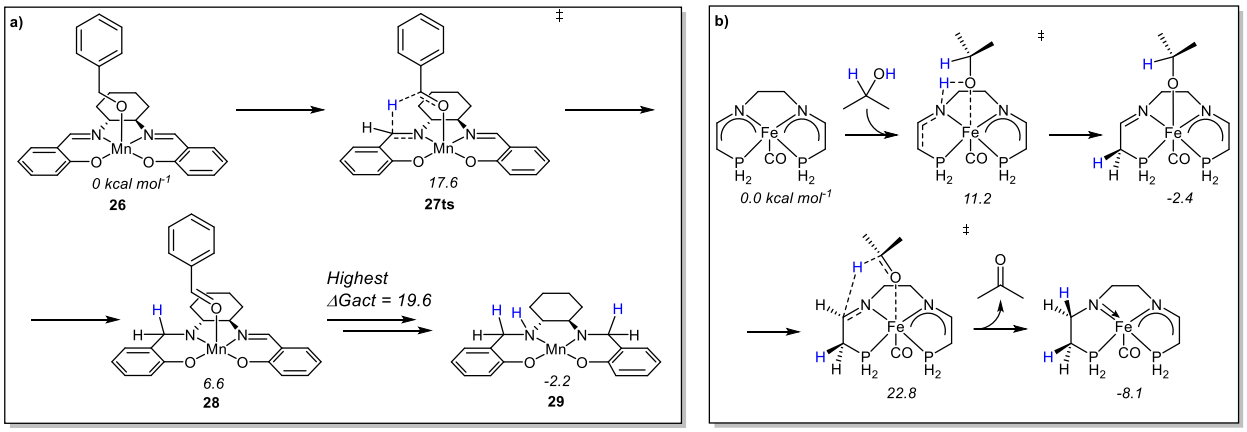


Figure 4.2. Hammett plot for the imination of *para*-substituted benzyl alcohols.

Density functional theory calculations (work by Professor Mårten S. G. Ahlquist)

To further understand the mechanism, density functional theory (DFT) calculations were used to estimate the Gibbs free energies of possible intermediates and transition states. This work was done in collaboration with Professor Mårten S. G. Ahlquist from KTH Royal Institute of Technology in Stockholm, who did all the calculations. The starting point was the Mn(salen)OBn complex **26**, where Cl has been replaced by a benzylic alkoxide (Scheme **4.16a**). This transformation involves the elimination of HCl, which is possible under the basic conditions. In fact, an experiment in the absence of a base (complex **19** and benzyl alcohol) gave no conversion at all, while the absence of the amine (complex **19**, benzyl alcohol and Ca_3N_2) resulted in 20% benzyl benzoate. The initial idea was that complex **26** undergoes β-hydride elimination. However, the activation energy for this process was found to be prohibitively high (at 37.9 kcal mol^{-1} relative to **26**), which is partly due to the lack of an available coordination site. Instead, an alternative reaction was found, where the hydride is transferred from the benzylic carbon to the imine carbon of the salen ligand. The activation energy was merely 17.6 kcal mol^{-1} and the product complex **28**

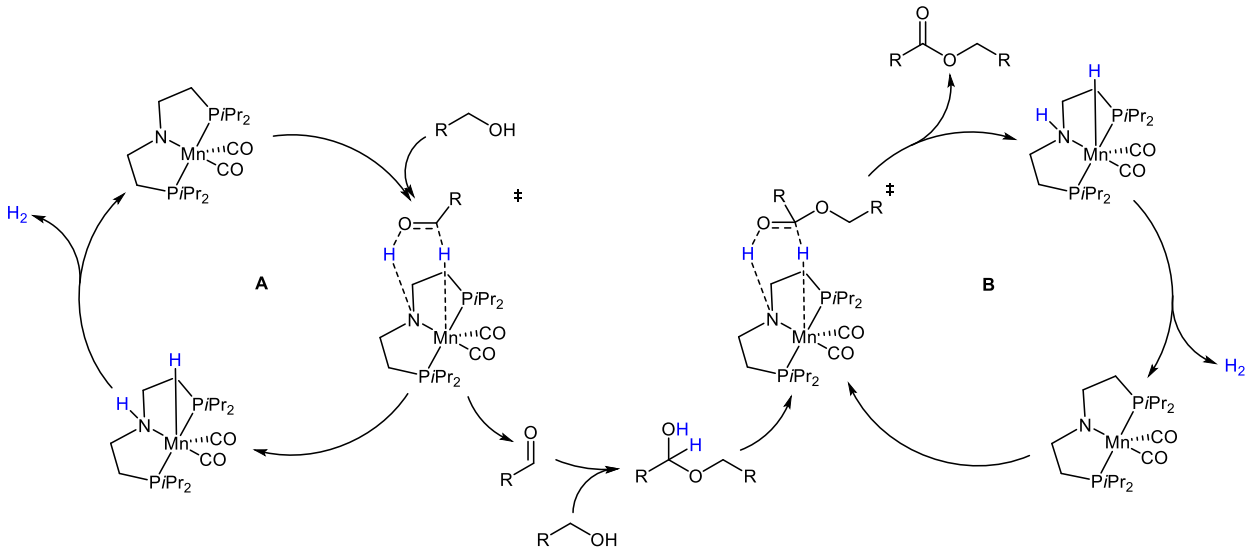
is at 6.6 kcal mol^{-1}. A similar pathway has been identified in the activation of (PNNP)Fe(II) eneamido complexes with isopropanol[167] (Figure **4.16b**). The product benzaldehyde is then replaced by benzyl alcohol, from which a proton is transferred to the amide nitrogen of the reduced salen ligand. The resulting complex where one imine of the salen is hydrogenated is at -5.2 kcal mol^{-1} relative to **26**. The lowest activation energy found from the hydrogenated intermediates was for another hydride transfer to the second imine of the salen with a transition state at 14.5 kcal mol^{-1}. After complete dissociation of benzaldehyde a key species **29** is formed, where one imine is hydrogenated and the other is reduced giving an amide ligand.[118]



Scheme 4.16. a) Activation of Mn(III)(salen)OBn to form the active amido complex, b) Activation of PNNP(Fe(II)) eneamido complex with isopropanol.[167]

The proposed catalytic cycle (work by Professor Mårten S. G. Ahlquist)

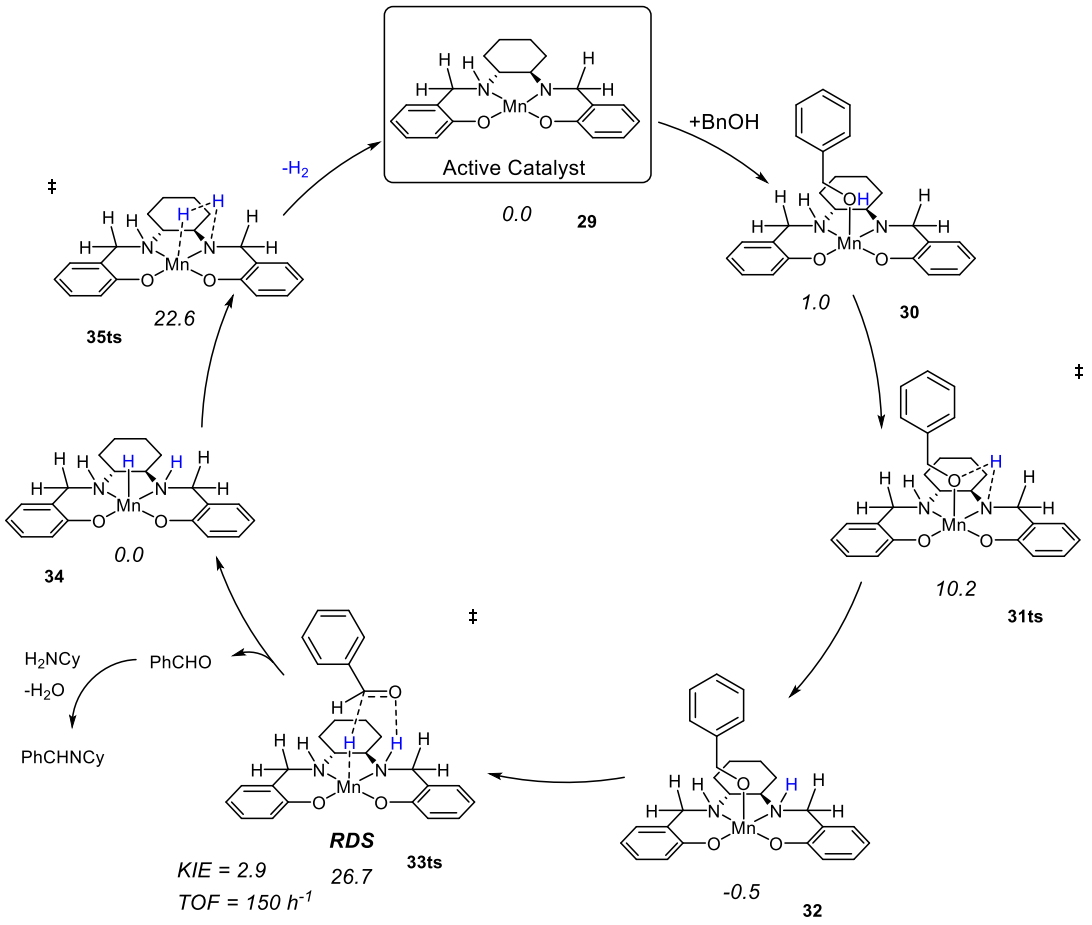
The key species **29** resembles intermediates from alcohol dehydrogenations with (PNP)Ru(II),[168] (PNP)Mn(I),[129] (PNNP)Fe(II)[169] and (PNP)Ir(III)[170] catalysts, which have an amide ligand that can act as a Brønsted base and a metal center that can serve as a hydride acceptor giving rise to bifunctional catalysts capable of MLC pathways. They have all been proposed to react via an outer-sphere hydrogen transfer mechanism. The main difference is the metal and the oxidation state, which in the current case is manganese(III).[118] The mechanism for alcohol dehydrogenation with (PNP)Mn(I)[129] is shown in Scheme **4.17**.



Scheme 4.17. Proposed mechanism for the (PNP)Mn(I) ester synthesis.[129]

The same outer-sphere hydrogen transfer was identified here and the activation energy is 26.7 kcal mol^{-1} relative to **29** and 27.2 kcal mol^{-1} relative to **32** (Scheme **4.18**), which corresponds to a turnover frequency (TOF) of 83 h^{-1} at the reaction conditions. After the formation of the manganese(III) hydride intermediate **34**, benzaldehyde is assumed to react irreversibly with the amine. From complex **34** the formation of hydrogen gas requires an activation energy of 22.6 kcal mol^{-1}, in a step that regenerates the active catalyst **29**.[118]

The calculated KIE of this reaction is 2.9, which is in reasonable agreement with the experimental value of 2.3. Finally, the relative rates of the *para*-substituted benzyl alcohols used in the experimental study were calculated from the pre-reactive complex **32** and an excellent agreement was found with the experimental result giving essentially the same ρ values (Figure **4.3**).[118]



Scheme 4.18. Proposed catalytic cycle and relative Gibbs free energies for the Mn(III)salen catalyzed imine synthesis.

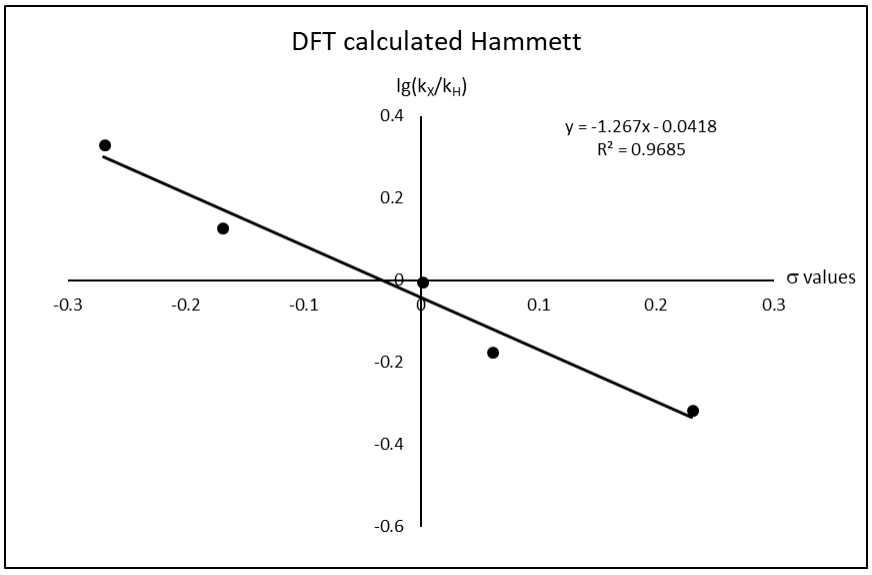
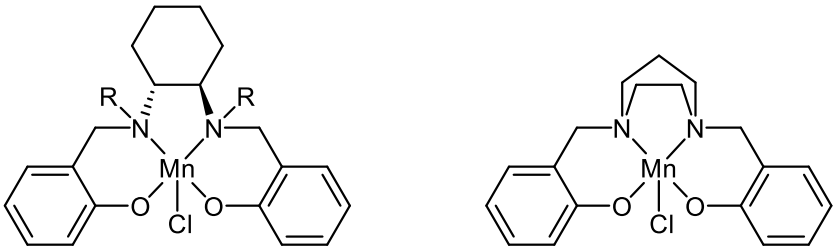


Figure 4.3. Hammett plot calculated by DFT.

Validation of MLC pathway

The proposed mechanism indicates that the Schiff base functionality of the salen ligand is crucial for the reactivity, suggesting a MLC pathway. To investigate this hypothesis further, three more complexes were prepared (Scheme **4.19**). The corresponding salan complex **36** resembles the proposed active catalyst **29**, whereas the ligands of complex **37** and **38** do not possess the Schiff base functionality and should, in theory, not give any conversion into the imine, if the hypothesis is correct. Complex **36**-**38** were investigated as catalysts for the dehydrogenative coupling of benzyl alcohol and cyclohexylamine under the same conditions as in Table **4.1** to be able to compare the them with the previously tested complexes (Table **4.6**).

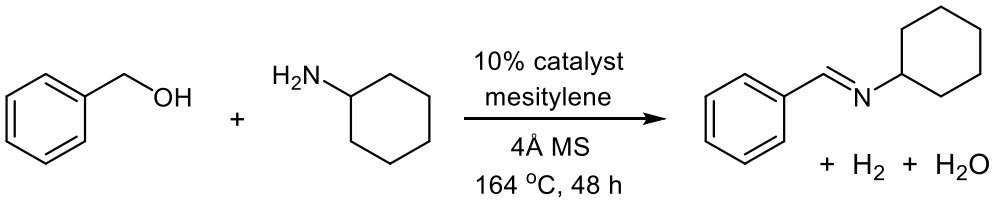


36: R = H
37: R = CH_3

38

Scheme 4.19. Manganese(iii) complexes used in validation of MLC pathway.

Table 4.6. Dehydrogenation with manganese(III) salen/salan complexes



entry[a]	catalyst	BnOH conversion (%)[b]	imine yield (%)[b]
1	**36**	47	12[c]
2	**37**	10	2
3	**38**	50	37

[a]Conditions: BnOH (1 mmol), $CyNH_2$ (1 mmol), catalyst (0.1 mmol), 4Å MS (150 mg), mesitylene (4 mL), reflux, 48 h. [b]Determined by GC-MS with tetradecane as internal standard. [c]Traces of benzyl benzoate was also formed.

Notably, complex **36** furnished some conversion into the imine (entry 1), which may indicate that the Schiff base functionality in the salen ligand plays an important role in the mechanism. However, the yield was significantly lower as compared to the yield with catalyst **19** (Table **4.1**, entry 2). When the imination with 5% of the salan complex **36** was repeated with *t*-BuOK as the base, a 56% yield was obtained of the imine. This result can be explained by elimination of HCl from **36** to afford the catalytically active species **29**. Similar eliminations of hydrogen halides under basic conditions have been described with (PNP)Mn(I), (PNP)Ru(II) and (PNNP)Fe(II) complexes to form the corresponding amido complexes.[123,171,172] The somewhat still lower yield of the imine with complex **36** may be explained by the fact that the HCl elimination from this complex does not seem to be very facile, since no detectable amount of the key species **29** was observed by LC-MS, when complex **36** was refluxed in toluene with stoichiometric amounts of *t*-BuOK. Notably, a post analysis by LC-MS of the imination with salan complex **36** showed the formation of complex **19** as the main manganese species together with other minor components of some unidentified complexes (Figure **4.4)**. None of the starting complex **36** could be detected after the imination. When the same experiment was carried out with salen complex **19**, only unchanged complex **19** was observed. This observation shows that a salan complex can be converted into the corresponding salen complex under the reaction conditions and explains why salen complex **19** is almost fully recovered after the reaction. So far, however, a pathway by which hydrogen is eliminated from a salan complex to afford the salen compound has not been identified.[118]

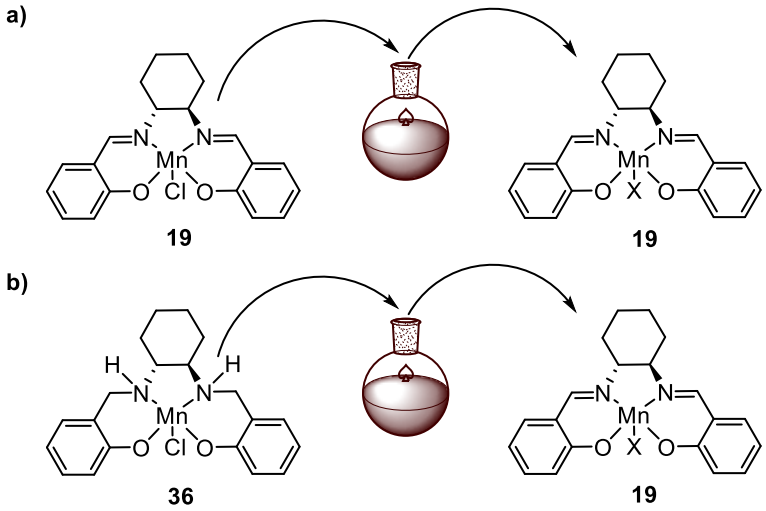


Figure 4.4. Isolation and analysis of catalyst a) **19** and b) **36** post reaction.

Low to moderate conversion and yield of the imine was obtained with both complex **38** and **39**, so a metal-ligand bifunctional pathway cannot be concluded from these results.

At last, the salen complex was isolated after reaction with $PhCD_2OH$ and cyclohexylamine. Analysis by LC-MS showed incorporation of two deuterium atoms. The re-isolated complex was treated with an excess amount of hydrochloric acid to perform a decomplexation followed by hydrolysis of the imines in the ligand, yielding the parent salicylaldehyde and amine. After extraction with EtOAc, analysis by ^{1}H-NMR revealed that the obtained aldehyde was salicylaldehyde-α-d_1. From this it can be concluded, that the isolated complex received one deuterium atom on each of the Schiff base carbons incorporated as would be expected from the proposed mechanism[118] (Figure **4.5**).

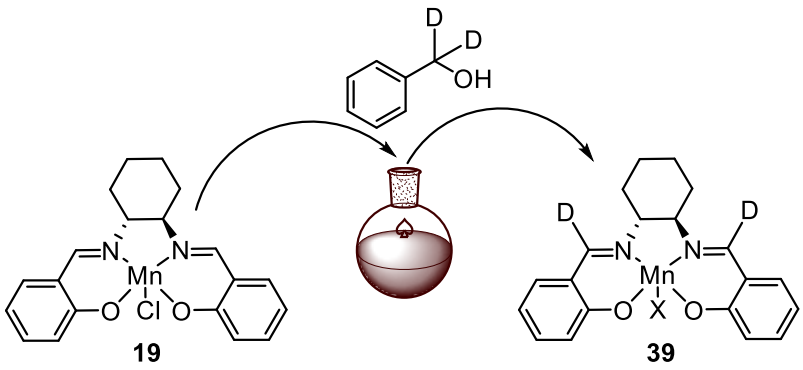


Figure 4.5. Incorporation of deuterium atoms at the Schiff base carbons in the ligand of catalyst **19** post reaction.

In the attempt to validate the MLC pathway experimentally, mixed results were obtained. Anyway, we strongly believe that the mechanism involves a bifunctional pathway and that the proposed catalytic cycle is a very good suggestion.

At last, it should be mentioned that complex **19** was analyzed by inductively coupled plasma mass spectrometry (ICP-MS) for traces of other metals known to perform alcohol dehydrogenations, since studies have shown that some coupling reactions performed by manganese catalysts are most likely mediated by traces of other elements. However, none of these elements could be detected beyond their detection limit.[118]

4.3 Project conclusion

In summary, a new catalyst for the acceptorless dehydrogenation of alcohols has been described. The manganese(III) salen complex **19** mediates the formation of imines from alcohols and amines with the liberation of hydrogen gas. The reaction can be performed with different alcohols and amines and can be extended to the synthesis of pyrroles. Complex **19** can be recovered from the reaction and used again without significantly affecting the catalytic activity. The mechanism is believed to involve a bifunctional pathway, where both the metal and the ligand participates in the dehydrogenation reaction.[118] This constitutes the very first example of a manganese(III) catalyst for acceptorless alcohol dehydrogenation. This discovery will probably spur much interest in the development of new transformations with hydrogen gas and manganese(III) catalysts.[118]

4.4 Experimental section [118]

4.4.1 General experimental methods

All commercial reagents were purchased from Sigma-Aldrich, Strem Chemicals, Fluorochem or abcr and used as received. NMR spectra were recorded at 400 MHz for ^{1}H-NMR and 101 MHz for ^{13}C-NMR on a Bruker Ascend 400 MHz spectrometer. Chemical shift values (δ) are reported in ppm relative to the residual solvent signal in $CDCl_3$ (δ_H 7.26 ppm, δ_C 77.2 ppm) while coupling constants (*J*) are given in Hz. High Resolution mass spectra were recorded using ESI with TOF detection. GC-MS was carried out on a Shimadzu GCMS-QP2010S instrument fitted with an Equity 5, 30 m×0.25 mm×0.25 μm column. Ionisation was performed by electronic impact (EI, 70 eV) and helium as the carrier gas. LC-MS was carried out on a Waters AQUITY UPLC system equipped with a PDA and SQD electrospray detector and fitted with a Thermo accucore C18, 2.6 μm, 2.1×50 mm column. Flash column chromatography was performed using silica gel 60 (0.035-0.070 mm particle size) saturated with Et_3N. Elemental analysis was performed by Mikrolab Kolbe, Germany. Mesitylene, 1,4-dioxane, diglyme, *o*-xylene, *p*-cymene and heptane were dried over molecular sieves (4 Å) while toluene was obtained by using a Pure Solv™ Micro solvent purification system. The water content of the solvents and liquid reagents was measured on a Karl-Fischer apparatus. All experiments were carried out under a nitrogen flow using Schlenk flask techniques except from the synthesis of catalysts.

4.4.2 General procedure for imine synthesis

Manganese complex **19** (20.6 mg, 0.05 mmol) and Ca_3N_2 (24.8 mg, 0.167 mmol) were placed in an oven-dried tube, where after it was placed in a carousel. Vacuum was applied and the flask was then filled with nitrogen gas (repeated three times). Anhydrous toluene (4 mL) was added and the reaction mixture was heated to reflux. Alcohol (1 mmol), amine (1 mmol) and tetradecane (0.5 mmol as internal standard) were added by a syringe, and the reaction was refluxed with stirring under a flow of nitrogen for 48 h. The mixture was cooled to room temperature and the solvent removed in vacuo. The crude product was purified by silica gel column chromatography (hexane with 2% Et_3N) to afford the desired imine or pyrrole.

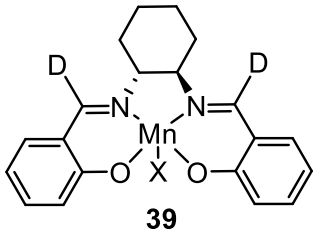
4.4.3 Gas development

Manganese complex **19** (20.6 mg, 0.05 mmol) was placed in an oven-dried Schlenk tube. The tube was subjected to vacuum and then filled with nitrogen gas (repeated three times). Freshly degassed, anhydrous toluene (4 mL) was added and the reaction mixture was heated to reflux. Benzyl alcohol (108 mg, 1 mmol), cyclohexylamine (99.0 mg, 1 mmol) and tetradecane (99.0 mg, 0.5 mmol, internal standard) were then added and the reaction tube was connected to a burette filled with water. The bottom of the burette was further connected to a water reservoir. The reaction mixture was refluxed for 48 h after which 18 mL (0.73 mmol) of gas was collected in the burette. A GC sample of the reaction mixture showed 78% yield of the imine and full conversion of the alcohol and the amine. The identity of the gas was established from a ^{1}H-NMR spectrum in toluene-d_8 showing a signal of H_2 at 4.51 ppm.

4.4.4 Deuterium labelling study

Benzyl alcohol-α,α-d_2 (110 mg, 1 mmol) and cyclohexylamine (99.0 mg, 1 mmol) were placed in an oven-dried tube and subjected to the imination reaction following the general procedure for imine synthesis. After purification of the product imine, examination of the ^{1}H-NMR revealed that the product imine was obtained as a pure deuterium-labeled imine and no hydrogen/deuterium scrambling had occurred.

The reaction was repeated and the catalyst was isolated after the reaction. LC-MS showed the same retention time as complex **19** and the molecular mass had increased by 2. The re-isolated complex was hydrolyzed with an excess amount of aqueous hydrochloric acid to yield the parent salicylaldehyde of the ligand. Examination of the ^{1}H-NMR revealed that the obtained aldehyde was salicylaldehyde-α-d_1 and the re-isolated catalyst is therefore **39**.



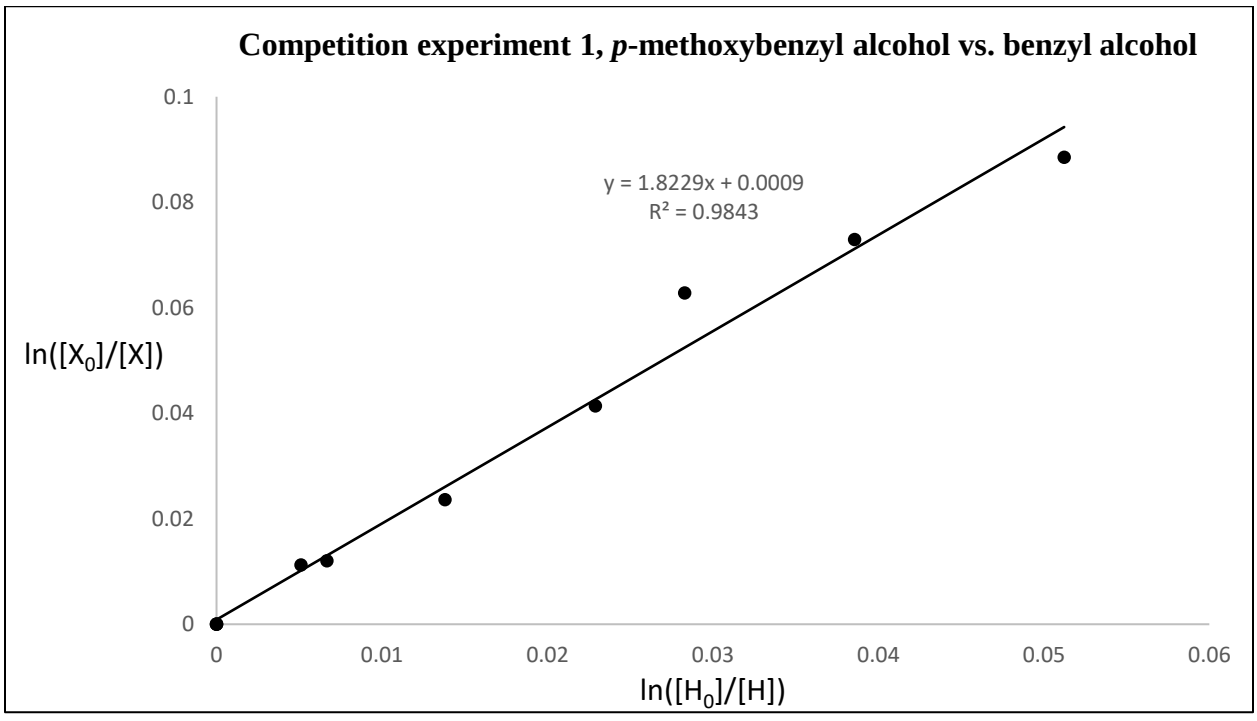
39

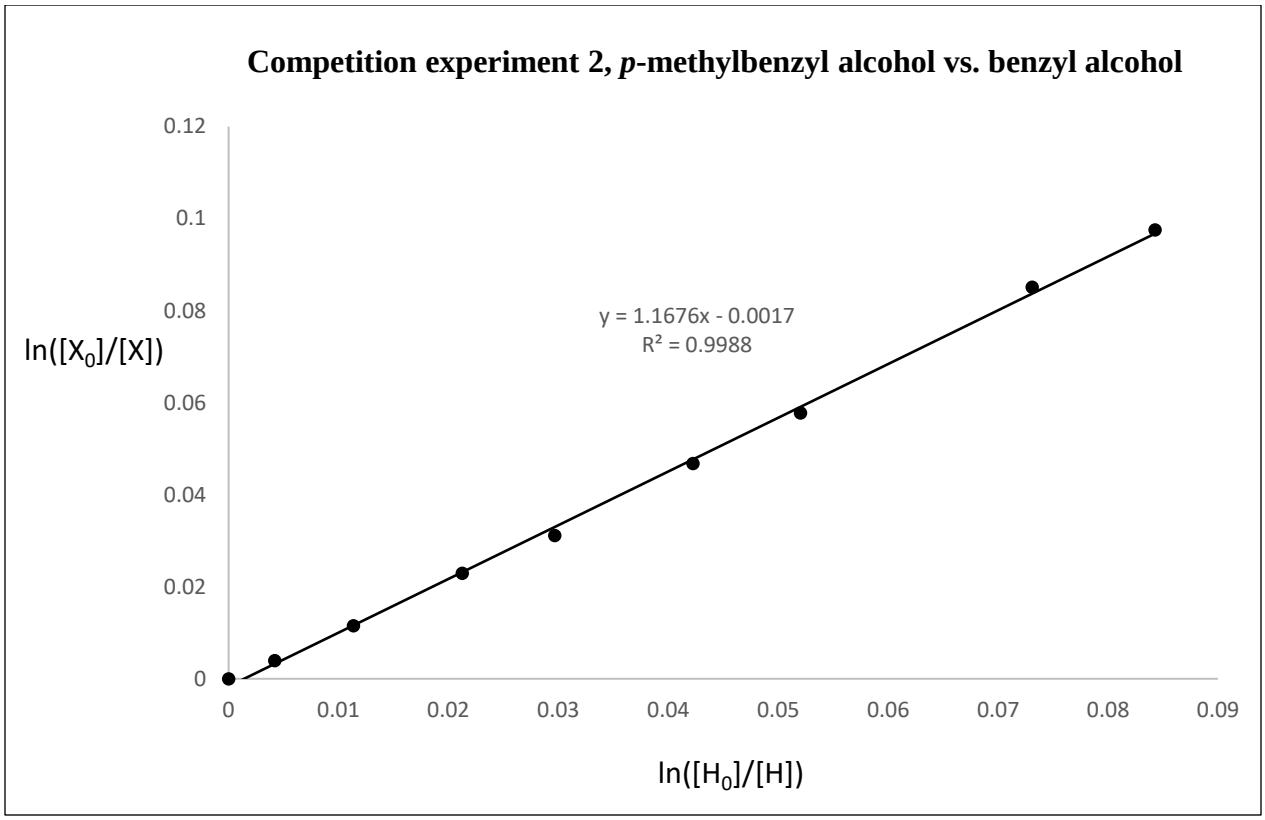
4.4.5 Determination of deuterium isotope effect

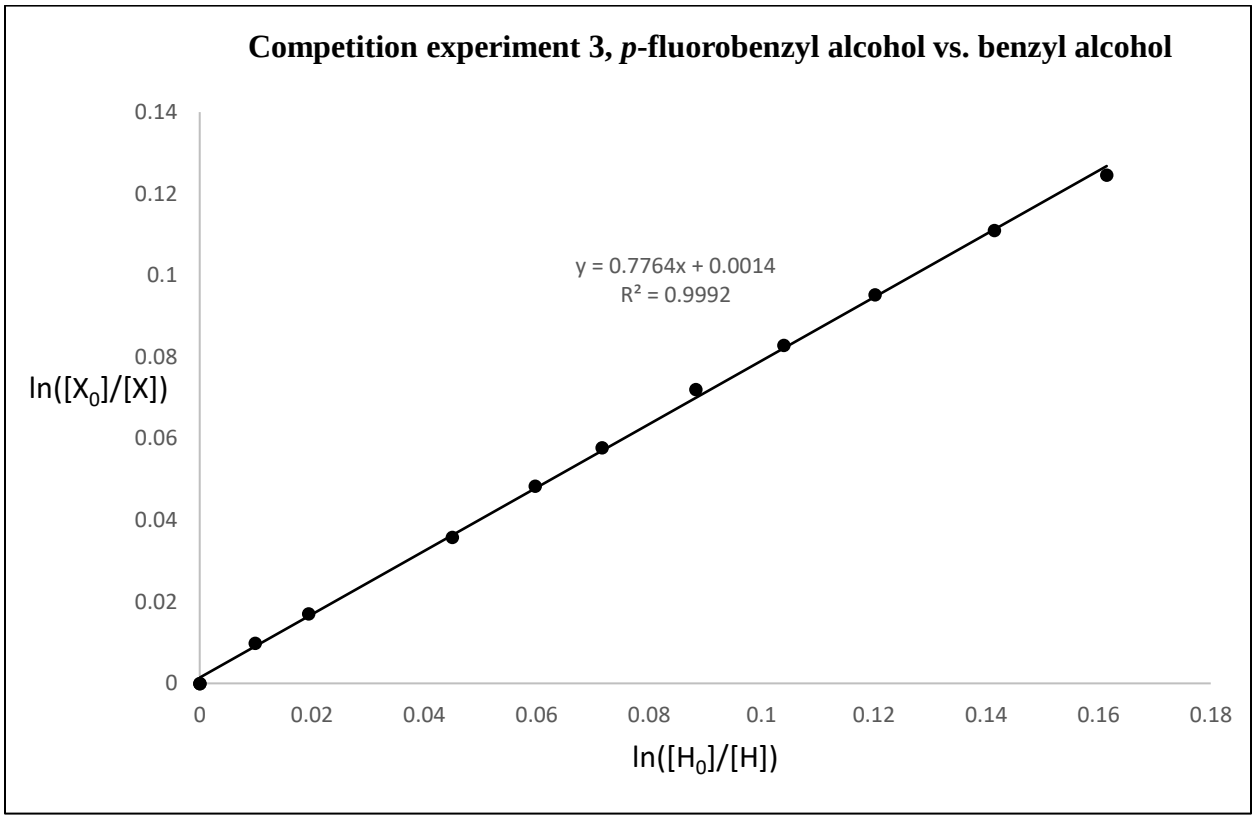
Benzyl alcohol (108 mg, 1 mmol) and cyclohexylamine (99.0 mg, 1 mmol) were placed in an oven-dried tube and subjected to the imination reaction following the general procedure for imine synthesis. For 5 h, a sample of 50 μL was taken out every 30 minutes, transferred to a GC vial, diluted to 1 mL with diethyl ether and then subjected to GC-MS analysis to follow the formation of *N*-benzylidenecyclohexylamine and determine the initial rate (r). The same procedure was repeated using benzyl alcohol-α,α-d_2 (110 mg, 1 mmol) instead of non-deuterated benzyl alcohol. The initial rate for the reaction of benzyl alcohol was $r_H = 7.00\ 10^{-4}$ M/min The initial rate for the reaction of benzyl alcohol-α,α-d_2 was $r_D = 3.00\ 10^{-4}$ M/min The isotope effect was $k_H/k_D = 2.3$.

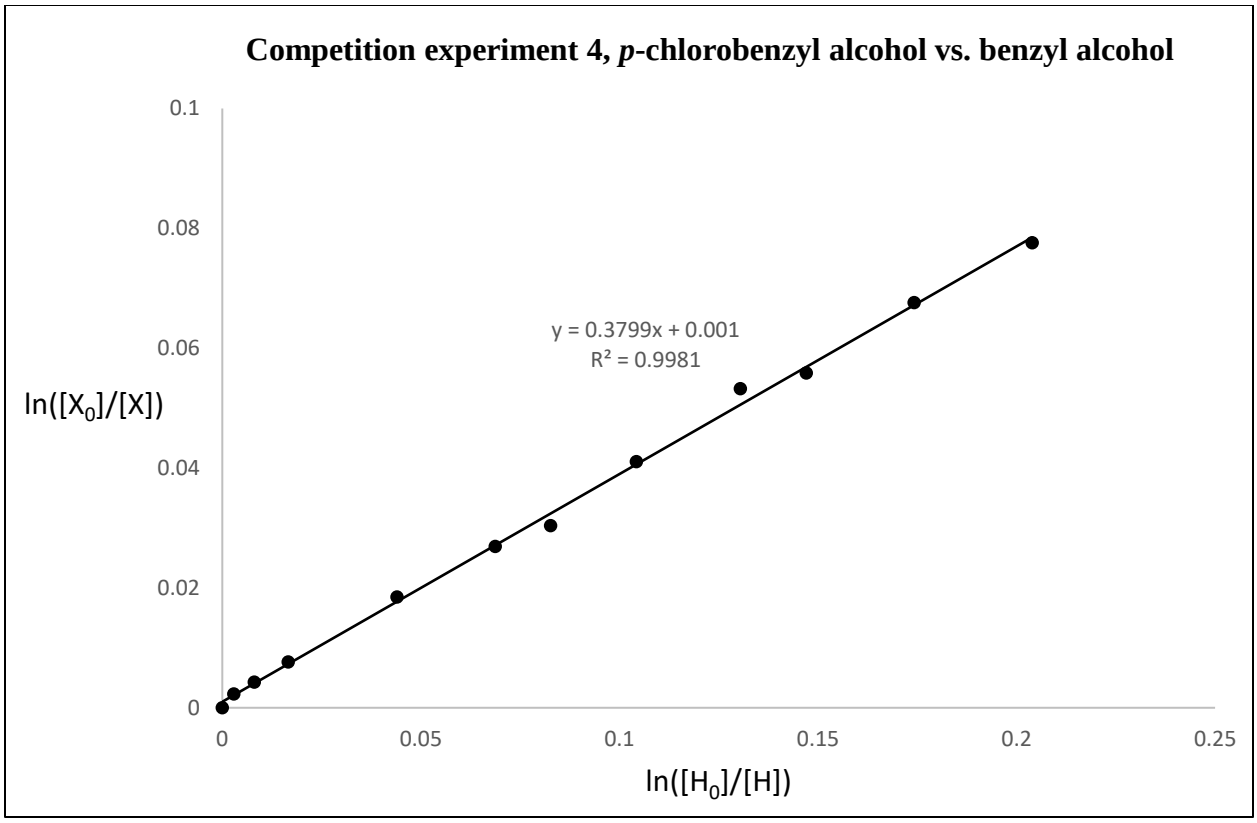
4.4.6 Hammett study

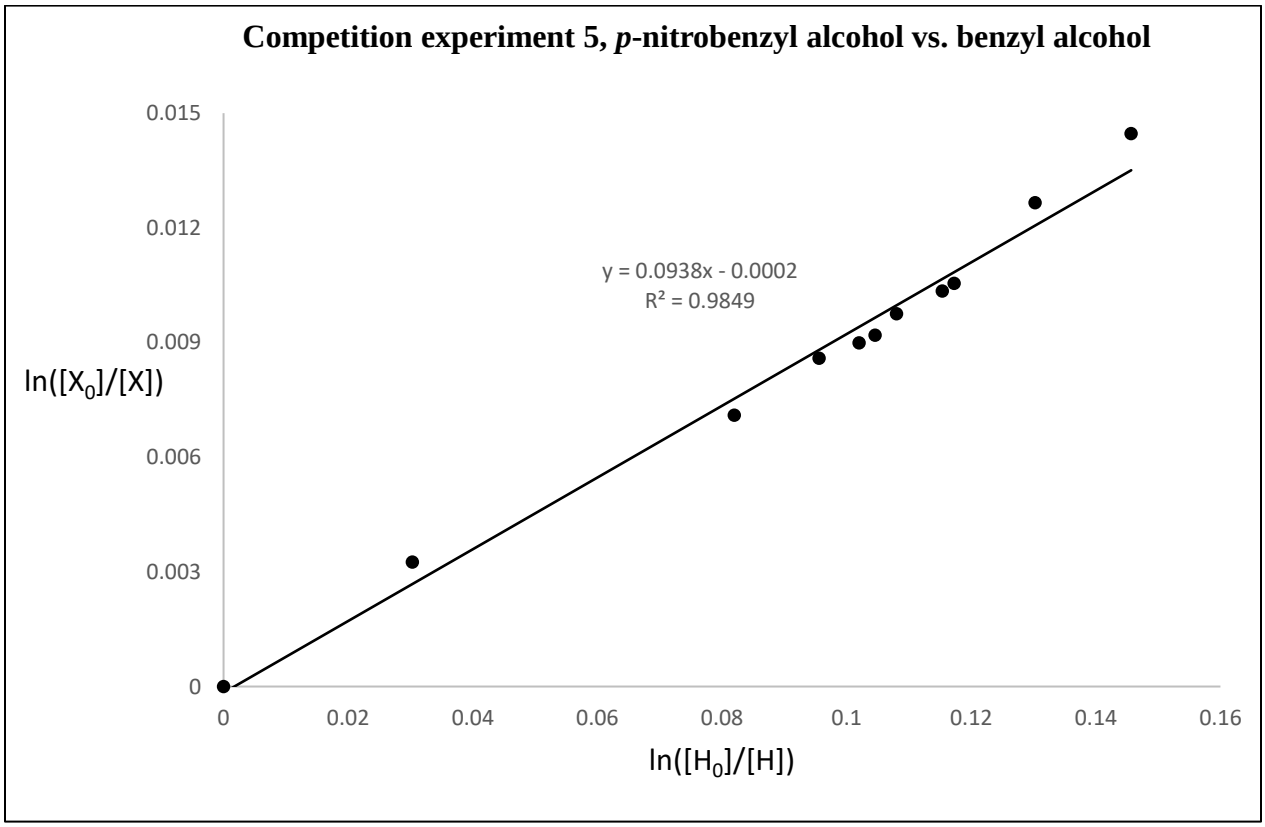
Benzyl alcohol (54.0 mg, 0.5 mmol), 4-substituted benzyl alcohol (0.5 mmol) and cyclohexylamine (99.0 mg, 1.0 mmol) were placed in an oven-dried tube and subjected to the imination reaction following the general procedure for imine synthesis. For 5 h, a sample of 50 μL was taken out every 30 minutes, transferred to a GC vial, diluted to 1 mL with diethyl ether and then subjected to GC-MS analysis to follow the formation of *N*-benzylidenecyclohexylamine and the 4-substituted *N*-benzylidenecyclohexylamine to determine k_{rel}.

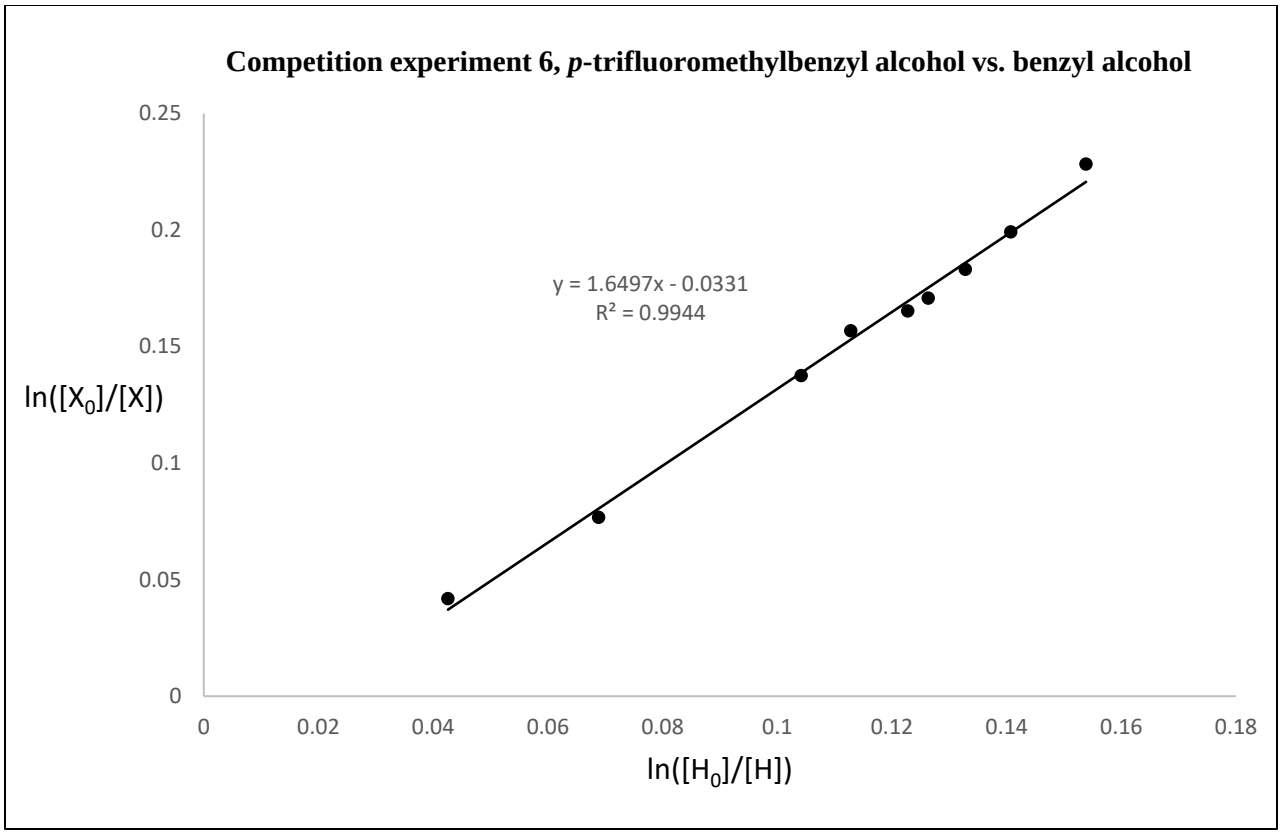



Competition experiment 2, p-methylbenzyl alcohol vs. benzyl alcohol
y = 1.1676x - 0.0017
R² = 0.9988
ln([X0]/[X])
ln([H0]/[H])
0.12
0.1
0.08
0.06
0.04
0.02
0
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09

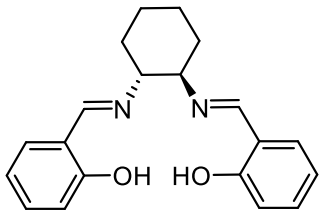

Competition experiment 3, p-fluorobenzyl alcohol vs. benzyl alcohol
y = 0.7764x + 0.0014
R² = 0.9992
ln([X0]/[X])
ln([H0]/[H])
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18


Competition experiment 4, p-chlorobenzyl alcohol vs. benzyl alcohol
y = 0.3799x + 0.001
R² = 0.9981
ln([X0]/[X])
ln([H0]/[H])
0.1
0.08
0.06
0.04
0.02
0
0
0.05
0.1
0.15
0.2
0.25


Competition experiment 5, p-nitrobenzyl alcohol vs. benzyl alcohol
y = 0.0938x - 0.0002
R² = 0.9849
ln([X0]/[X])
ln([H0]/[H])
0.015
0.012
0.009
0.006
0.003
0
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16



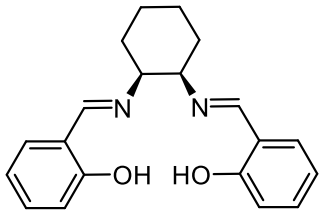
4.4.7 Procedures for ligand synthesis



(1*R*,2*R*)-*N*,*N'*-Bis(salicylidene)-1,2-cyclohexanediamine

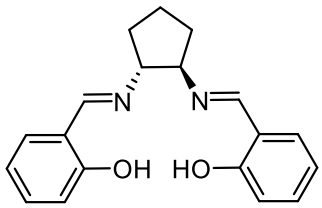
A mixture of (1*R*, 2*R*)-(+)-1,2-diaminocyclohexane L-tartrate (1.00 g, 3.8 mmol), K_2CO_3 (525 mg, 3.8 mmol) and water (2.5 mL) was stirred until complete dissolution, followed by addition of methanol (20 mL) was added. The reaction mixture was heated to reflux and a solution of salicylaldehyde (0.80 mL, 7.6 mmol) in methanol (8 mL) was added over 30 min. The reaction mixture was refluxed for an additional 4 h and was cooled to room temperature. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (15 mL), washed with water (8 mL), dried (Na_2SO_4) and concentrated in vacuo to give the desired ligand as a yellow oil. Yield:

1.21 g (99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.26 (s, 2H), 7.26-7.21 (m, 2H), 7.15 (dd, *J* = 7.7, 1.7 Hz, 2H), 6.88 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.79 (td, *J* = 7.6, 1.1 Hz, 2H), 3.37-3.25 (m, 2H), 1.98-1.84 (m, 4H), 1.78-1.67 (m, 2H), 1.54-1.41 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 164.1, 161.1, 132.3, 131.6, 118.8, 118.7, 116.9, 72.8, 33.2, 24.3. NMR data are in accordance with literature values.[173]



(1*S*,2*R*)-*N*,*N*'-Bis(salicylidene)-1,2-cyclohexanediamine

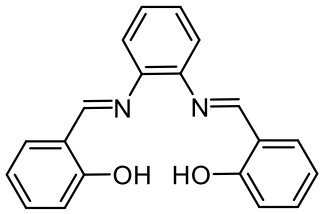
Cis-1,2-diaminocyclohexane (500 mg, 4.38 mmol) was refluxed with salicylaldehyde (0.93 mL, 8.76 mmol) in ethanol (12 mL) for 2 h. The reaction mixture was kept in the refrigerator overnight, and the precipitated yellow crystals were collected by filtration and dried under vacuum. Yield: 1.15 g (82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 (s, 2H), 7.23-7.18 (m, 2H), 7.16 (dd, *J* = 7.6, 1.7 Hz, 2H), 6.84 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.77 (td, *J* = 7.5, 1.1 Hz, 2H), 3.55-3.53 (m, 2H), 1.97-1.77 (m, 4H), 1.74-1.65 (m, 2H), 1.56-1.46 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 164.3, 161.4, 132.4, 131.6, 118.9, 118.6, 117.1, 69.5, 30.8, 22.6. NMR data are in accordance with literature values.[174]



(1*R*,2*R*)-*N*,*N*'-Bis(salicylidene)-1,2-cyclopentanediamine

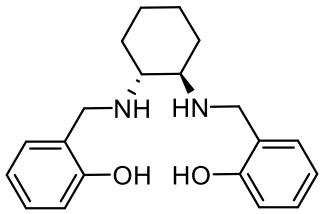
A mixture of (1*R*, 2*R*)-*trans*-1,2-diaminocyclopentane dihydrochloride (75.0 mg, 0.43 mmol), K_2CO_3 59.0 mg, 0.43 mmol) and water (0.50 mL) was stirred until complete dissolution, followed by addition of methanol (3 mL) was added. The reaction mixture was heated to 65 ºC and a solution of salicylaldehyde (0.01 mL, 0.86 mmol) in methanol (1 mL) was added over 30 min. The reaction mixture was refluxed for additional 4 h and was cooled to room temperature. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (2 mL), washed with water (2

x 0.5 mL), dried (Na_2SO_4) and concentrated in vacuo to give the desired ligand as a yellow oil. Yield: 20 mg (15%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.28 (s, 2H), 7.29 (ddd, *J* = 8.7, 7.3, 1.7 Hz, 2H), 7.19 (dd, *J* = 7.6, 1.7 Hz, 2H), 6.95 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.84 (td, *J* = 7.4, 1.1 Hz, 2H), 3.72-3.79 (m, 2H), 2.27-2.19 (m, 2H), 2.02-1.94 (m, 4H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 164.7, 132.4, 131.5, 119.9, 118.7, 117.6, 116.9, 76.5, 32.9, 21.9.



***N,N'*-Bis(salicylidene)-1,2-benzenediamine**

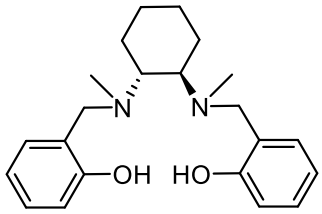
o-Phenylenediamine (1.08 g, 10 mmol) was dissolved in ethanol (25 mL). Salicylaldehyde (2.44 g, 20 mmol) dissolved in ethanol (25 mL) was added dropwise to the solution over 5 min and the reaction was heated to reflux for 2½ h. The mixture was allowed to cool to room temperature, and the precipitated orange crystals were collected by filtration, washed with cold ethanol and dried under vacuum. Yield: 822 mg (26%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.65 (s, 2H), 7.41-7.33 (m, 6H), 7.27-7.24 (m, 2H), 7.07 (d, *J* = 8.2, 1.0 Hz, 2H), 6.93 (td, *J* = 7.5, 1.1 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 163.9, 161.5, 142.5, 133.7, 132.6, 127.9, 119.9, 119.3, 119.2, 117.7. NMR data are in accordance with literature values.[175]



(1*R*,2*R*)-*N,N'*-Bis(2-hydroxybenzyl)-1,2-cyclohexanediamine

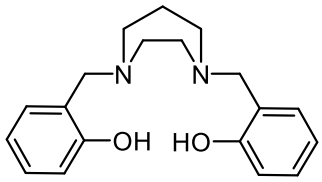
Sodium borohydride (247 mg, 6.5 mmol) was added over 30 min to a solution of (1*R*,2*R*)-*N,N'*-bis(salicylidene)-1,2-cyclohexanediamine (1.00 g, 3.1 mmol) in methanol (12 mL) at 0 ºC. The reaction mixture allowed to warm to room temperature and stirring was continued for 1 h. After cooling to room temperature, water (15 mL) was added and the mixture was extracted with dichloromethane (3 × 12 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to afford the desired ligand as a white solid. Yield: 515 mg (51%). ^{1}H-NMR (400 MHz,

$CDCl_3$) δ ppm: 7.17 (td, *J* = 7.8, 1.7 Hz, 2H), 6.98 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.85-6.75 (m, 4H), 4.10-3.87 (m, 4H), 2.49-2.40 (m, 2H), 2.21-2.10 (m, 2H), 1.79-1.65 (m, 2H), 1.28-1.16 (m, 4H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.0, 129.0, 128.5, 122.9, 119.4, 116.6, 59.8, 49.7, 30.5, 24.3. NMR data are in accordance with literature values.[173]



(1*R*,2*R*)- *N*,*N*'-Dimethyl-*N*,*N*'-bis(2-hydroxybenzyl)-1,2-cyclohexanediamine

n-BuLi (2.4 mL, 2.5 M solution in hexane, 6 mmol) was added dropwise to a solution of (1*R*,2*R*)-*N*,*N*'-Bis(2-hydroxybenzyl)-1,2-cyclohexanediamine (433 mg, 1.33 mmol) in 30 mL of THF at 0 ºC under an argon atmosphere. After being stirred for 1.5 h, the mixture was allowed to warm to ambient temperature. Iodomethane (0.39 mL, 6 mmol) was added slowly and stirring continued for another 6 h. Water (10 mL) was then added to quench the reaction and the aqueous layer separated and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was further purified by flash chromatography (0-20% EtOAc/hexane) to give the desired ligand as a white solid. Yield: 275 mg, 55% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.21-7.18 (m, 2H), 7.02-6.98 (m, 2H), 6.87-6.80 (m, 4H), 3.85 (d, *J* = 13 Hz, 2H), 3.65 (d, *J* = 13 Hz, 2H), 2.75-2.71 (m, 2H), 2.24 (s, 6H), 2.06-2.01 (m, 2H), 1.85-1.81 (m, 2H), 1.27-1.15 (m, 4H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.3, 129.5, 129.1, 122.4, 119.1, 116.5, 62.1, 57.1, 35.6, 25.4, 22.3. NMR data are in accordance with literature values.[176]

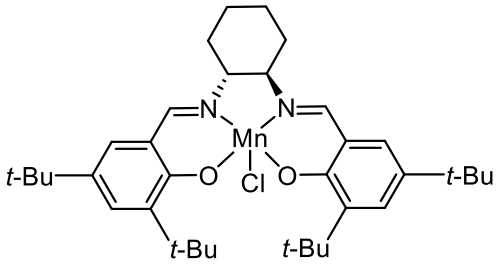


1,4-Bis(2-hydroxybenzyl)-1,4-diazepane

To a solution of salicylaldehyde (2.44 g, 20 mmol) in methanol (100 mL) was added homopiperazine (1.00 g, 10 mmol) and acetic acid (0.2 mL). $NaCNBH_3$ (1.26 g, 20 mmol) was

added dropwise to the resulting solution. After stirring for 3 days, the mixture was acidified (pH ≈ 1) by adding concentrated HCl and then evaporated to almost dryness under reduced pressure. The residue was dissolved in saturated aqueous solution of Na_2CO_3 (50 mL) and extracted with chloroform (3 x 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column purification (0-10% EtOAc/hexane) afforded the desired ligand as a yellow solid. Yield: 1.49 g (50%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.17 (td, *J* = 7.8, 1.7 Hz, 2H), 6.96 (dd, *J* = 7.6, 1.6 Hz, 2H), 6.83 (dd, *J* = 8.2, 1.2 Hz, 2H), 6.78 (td, *J* = 7.4, 1.2 Hz, 2H), 3.80 (s, 4H), 2.94-2.66 (m, 8H), 1.94 (p, *J* = 6.1 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.0, 129.1, 128.7, 121.8, 119.3, 116.3, 61.9, 54.7, 53.6, 26.8. NMR data are in accordance with literature values.[177]

4.4.8 Procedures for manganese(III) catalyst synthesis



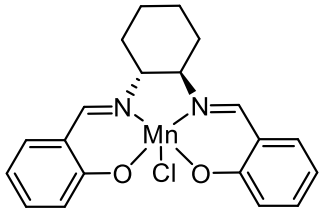
(1*R*,2*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (18)

$Mn(OAc)_2 \bullet 4H_2O$ (2.50 g, 10 mmol) was dissolved in EtOH (20 mL) and the mixture was heated to reflux temperature. A solution of (1*R*,2*R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (1.86 g, 3.33 mmol) in toluene (10 mL) is added in a slow stream over 45 min. The reaction mixture was stirred at reflux temperature for 3 h in the presence of air. A solution of saturated aqueous NaCl (4 mL) was added and the reaction mixture was allowed to cool to room temperature. The phases were separated and the organic solution was washed with water (3 x 25 mL) followed by saturated aqueous NaCl (20 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The dark brown solid was dissolved in dichloromethane (15 mL). Heptane (15 mL) was added and dichloromethane was removed by reduced pressure. After complete removal of dichloromethane, the brown slurry was stirred for 1 h at 5 ºC. The brown solid was collected by filtration and dried under vacuum at 60 ºC to yield the desired product as a dark brown

powder. Yield: 1.79 g (85%). ESI-HRMS, *m/z* = 600.3456, $[C_{36}H_{53}MnN_2O_2+H]^+$, calc. 600.3482. FTIR, *v*/cm^{-1}: 2950 s, 1606 vs, 1534 m, 1432 w, 1388 w, 1312 m, 1251 m, 1174 m, 837 w, 749 w, 542 w.[178]

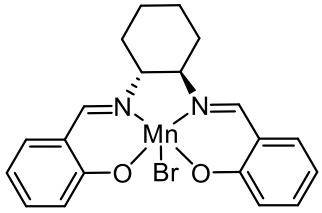
General procedure for synthesis of manganese complex 19-24 and 36-37

$MnCl_2 \bullet 4H_2O$, $MnBr_2$ or $Mn(OAc)_2 \bullet 4H_2O$ (3.3 mmol) and ligand (3.0 mmol) in EtOH (100 mL) were refluxed for 2 h in the presence of air. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure yielding a dark brown solid, which was recrystallized from EtOH and dried under vacuum to give the desired product.



(1*R*,2*R*)-*N*,*N'*-Bis(salicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (19)

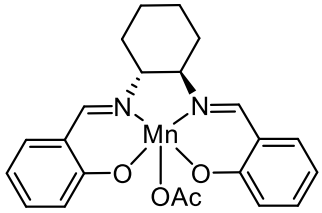
Following the general procedure for synthesis of manganese complexes with $MnCl_2 \bullet 4H_2O$, the catalyst was obtained as black crystals. Yield: 688 mg (53%). ESI-HRMS, *m/z* = 433.0477 $[M+Na]^+$, calc. 433.0594. FTIR, *v*/cm^{-1}: 2912 m, 1617 vs, 1597 vs, 1549 s, 1469 m, 1435 s, 1302 s, 1247 s, 1219 s, 1080 m, 982 m, 846 w, 730 w. Anal. calc.: C, 58.48; H, 4.91; Cl, 8.63; Mn, 13.37; N, 6.82. Found: C, 58.30; H, 4.83; Cl, 8.61; Mn, 13.29; N, 6.49. Trace metal analysis: Ag <2; Co <0.5; Cr <3; Cu <10; Fe <20; Mo <0.4; Ni <4; Zn <20; Au <1; Pd <1; Pt <1; Ir <1; Rh <1; Ru <1; Os <1 ppm.[179]



(1*R*,2*R*)-*N*,*N'*-Bis(salicylidene)-1,2-cyclohexanediaminomanganese(III) bromide (20)

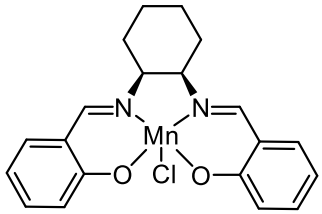
Following the general procedure for synthesis of manganese complexes with $MnBr_2$, the catalyst was obtained as a brown powder. Yield: 137 mg (10%). ESI-HRMS, *m/z* = 376.0937,

$[C_{20}H_{21}MnN_2O_2+H]^+$, calc. 376.0978. FTIR, *v*/cm^{-1}: 2938 m, 2852 m, 1614 vs, 1540 m, 1441 m, 1306 w, 1202 m, 1149 m, 904 w, 858 w, 811 w, 752 m, 624 m, 568 m, 424 w.[180]



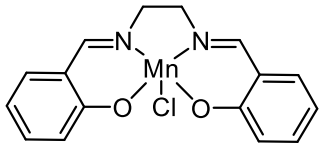
(1*R*,2*R*)-*N*,*N'*-Bis(salicylidene)-1,2-cyclohexanediaminomanganese(III) acetate (21)

Following the general procedure for synthesis of manganese complexes with $Mn(OAc)_2 \bullet 4H_2O$, the catalyst was obtained as a brown powder. Yield: 520 mg (40%). ESI-HRMS, *m/z* = 375.0935 $[C_{20}H_{20}MnN_2O_2]^+$, calc. 375.0905. FTIR, *v*/cm^{-1}: 2933 w, 2862 w, 1619 s, 1537 vs, 1441 s, 1308 m, 1199 m, 1147 m, 907 m, 809 m, 760 s, 622 m, 567 w, 425 w.[181]



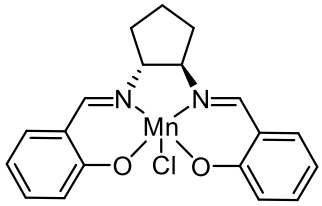
(1*S*,2*R*)-*N*,*N'*-Bis(salicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (22)

Following the general procedure for synthesis of manganese complexes with $MnCl_2 \bullet 4H_2O$, the catalyst was obtained as black crystals. Yield: 650 mg (50%). ESI-HRMS, *m/z* = 433.0520 $[M+Na]^+$, calc. 433.0594. FTIR, *v*/cm^{-1}: 2925 m, 1619 vs, 1599 vs, 1543 s, 1445 s, 1400 w, 1318 s, 1279 s, 1196 w, 1151 w, 902 w, 814 w, 747 s, 603 m, 432 w. Anal. calc.: C, 58.48; H, 4.91; Cl, 8.63; Mn, 13.37; N, 6.82. Found: C, 57.94; H, 4.97; Cl, 8.47; Mn, 13.51; N, 6.53.



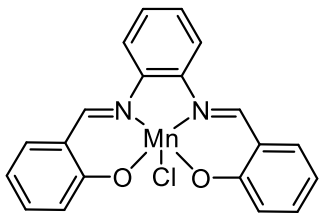
***N,N'*-Bis(salicylidene)ethylenediaminomanganese(III) chloride (23)**

Following the general procedure for synthesis of manganese complexes with $MnCl_2 \bullet 4H_2O$, the catalyst was obtained as black crystals. Yield: 438 g (41%). ESI-HRMS, *m/z* = 322.0471, $[C_{16}H_{15}MnN_2O_2+H]^+$, calc. 322.0509. FTIR, *v*/cm^{-1}: 1617 vs, 1595 vs, 1533 s, 1442 s, 1389 m, 1322 m, 1300 vs, 1274 s, 1197 m, 1147 m, 1125 m, 886 w, 796 s, 756 s, 621 s, 458 s.[179]



(1*R*,2*S*)-*N,N'*-Bis(salicylidene)-1,2-cyclopentanediaminomanganese(III) chloride (24)

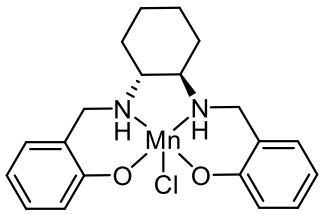
Following the general procedure for synthesis of manganese complexes, the catalyst was obtained as black crystals. Yield: 202 mg (17%). ESI-HRMS, *m/z* = 362.078659 $[C_{19}H_{19}MnN_2O_2+H]^+$, calc. 362.082149. FTIR, *v*/cm^{-1}: 2973 w, 2895 w, 1606 vs, 1581 s, 1539 vs, 1462 s, 1437 s, 1382 m, 1292 s, 1180 m, 1156 m, 1126 w, 1036 w, 915 w, 750 s, 532 w.



***N,N'*-Bis(salicylidene)-1,2-benzenediaminomanganese(III) chloride (25)**

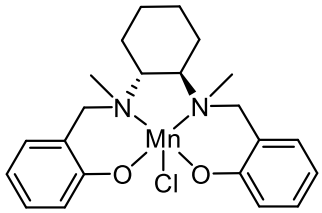
N,N'-Bis(salicylidene)-1,2-benzenediamine (500 mg, 1.60 mmol) was dissolved in EtOH (15 mL). $Mn(OAc)_2 \bullet 4H_2O$ (780 mg, 4.50 mmol) was added to the solution and the mixture was refluxed for 1 h. LiCl (200 mg, 4.70 mmol) was added and the reaction was refluxed for an additional 30 min. The mixture was allowed to cool to room temperature and the precipitated brown solid was collected, washed with cold EtOH and dried under vaccum. Yield: 226 mg (35%). ESI-HRMS,

m/z = 370.0471 $[C_{20}H_{15}MnN_2O_2+H]^+$, calc. 370.0508. FTIR, *v*/cm^{-1}: 1605 vs, 1580 vs, 1538 vs, 1462 m, 1438 m, 1383 m, 1290 m, 1179 m, 1153 m, 1035 w, 914 w, 750 s, 531 m.[182]



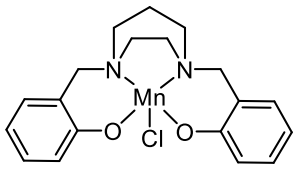
(1*R*,2*R*)-*N*,*N*'-Bis(2-hydroxybenzyl)-1,2-cyclohexanediaminomanganese(III) chloride (36)

Following the general procedure for synthesis of manganese complexes with $MnCl_2 \bullet 4H_2O$, the catalyst was obtained as a brown powder. Yield: 633 mg (51%). FTIR, *v*/cm^{-1}: 3344 s, 2937 m, 1602 vs, 1479 m, 1448 s, 1261 s, 1239 m, 754 m.



(1*R*,2*R*)-*N*,*N*'-Dimethyl-*N*,*N*'-bis(2-hydroxybenzyl)-1,2-cyclohexanediaminomanganese(III) chloride (37)

Following the general procedure for synthesis of manganese complexes, the catalyst was obtained as a brown powder. Yield: 755 mg (57%). FTIR, *v*/cm^{-1}: 2936 m, 1596 s, 1450 vs, 1268 s, 882 w, 755 m.

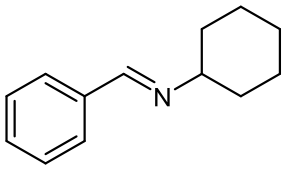


1,4-Bis(2-hydroxybenzyl)-1,4-diazepanomanganese chloride (38)

A solution of $MnCl_2 \bullet 4H_2O$ (162 mg, 1.00 mmol) in methanol (5 mL) was added to an acetonitrile solution of an equivalent amount of 1,4-bis(2-hydroxybenzyl)-1,4-diazepane (312 mg, 1.00 mmol) and triethylamine (200 mg, 2.0 mmol) in methanol (2 mL) was added. The solution was stirred for

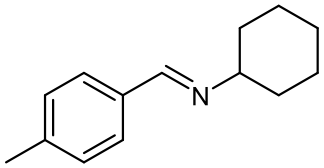
3 h. The dark blue colored precipitate obtained was filtered off, washed with cold methanol and dried in vacuo. Yield: 200 mg (50%). FTIR, $\tilde{\nu}$/cm^{-1}: 1593 m, 1474 s, 1449 s, 1263 s, 1110 w, 880 w, 746 m, 631 w, 589 w.[177]

4.7.9 Characterization data



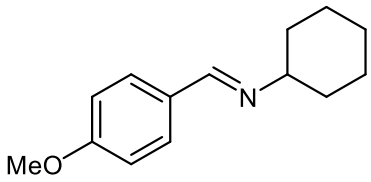
***N*-Benzylidenecyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 166 mg (89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.32 (s, 1H), 7.74-7.72 (m, 2H), 7.41-7.38 (m, 3H), 3.24-3.17 (m, 1H), 1.85-1.28 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.4, 136.4, 130.1, 128.3, 127.9, 69.8, 34.2, 25.5, 24.7. MS: *m/z* = 187 $[M]^+$. NMR data are in accordance with literature values.[94]



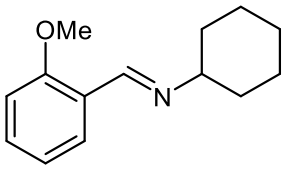
***N*-(4-Methylbenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 141 mg (70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.28 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 3.21-3.14 (m, 1H), 2.37 (s, 3H), 1.86-1.24 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.7, 140.7, 134.0, 129.3, 128.2, 70.1, 34.5, 25.8, 25.0, 21.6. MS: *m/z* = 201 $[M]^+$. NMR data are in accordance with literature values.[183]



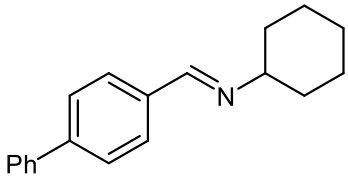
***N*-(4-Methoxybenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 180 mg (83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.24 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.18-3.11 (m, 1H), 1.86-1.16 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 161.5, 158.0, 132.0, 129.7, 114.0, 70.0, 55.4, 34.6, 25.8, 25.0. MS: *m/z* = 217 $[M]^+$. NMR data are in accordance with literature values.[94]



***N*-(2-Methoxybenzylidene)-cyclohexylamine**

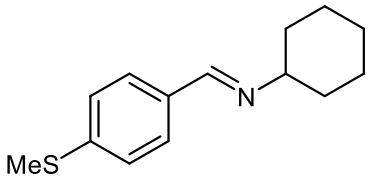
Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 195 mg (90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.74 (s, 1H), 7.94 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.45-7.30 (m, 1H), 7.02-6.82 (m, 2H), 3.86 (s, 3H), 3.25-3.17 (m, 1H), 1.83-1.22 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.7, 154.7, 131.6, 127.5, 125.2, 120.9, 111.0, 70.4, 55.6, 34.6, 25.8, 25.0. MS: *m/z* = 217 $[M]^+$. NMR data are in accordance with literature values.[184]



***N*-(4-Phenylbenzylidene)-cyclohexylamine**

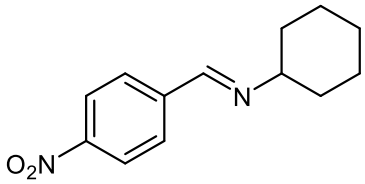
Following the general procedure for imine synthesis, the product was isolated as a pale yellow solid. Yield: 158 mg (60%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.36 (s, 1H), 7.87-7.77 (m, 2H), 7.67-7.56 (m, 4H), 7.49-7.30 (m, 3H), 3.27-3.18 (m, 1H), 1.87-1.23 (m, 10H). ^{13}C-NMR (101

MHz, $CDCl_3$) δ ppm: 158.3, 143.2, 140.7, 135.7, 128.9, 128.6, 127.8, 127.4, 127.3, 70.2, 34.5, 25.8, 25.0. MS: *m/z* = 263 $[M]^+$. NMR data are in accordance with literature values.[102]



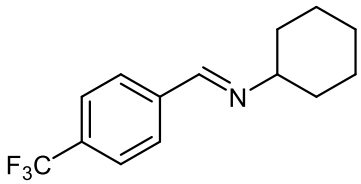
***N*-(4-Methylthiobenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a pale yellow solid. Yield: 140 mg (60%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.25 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.24 (m, 2H), 3.21-3.14 (m, 1H), 2.50 (s, 3H), 1.86-1.19 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.2, 129.0, 128.6, 126.0, 123.8, 70.0, 34.5, 25.8, 25.0, 15.5. MS: *m/z* = 234 $[M]^+$. NMR data are in accordance with literature values.[102]



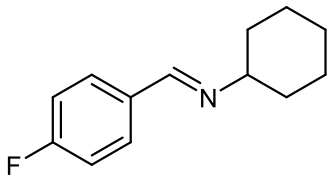
***N*-(4-Nitrobenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a pale yellow solid. Yield: 162 mg (70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.38 (s, 1H), 8.25 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 3.31-3.24 (m, 1H), 1.88-1.24 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 156.4, 149.0, 142.3, 128.8, 123.9, 70.3, 34.3, 25.7, 24.7. MS: *m/z* = 232 $[M]^+$. NMR data are in accordance with literature values.[185]



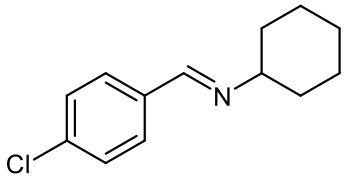
***N*-(4-trifluoromethylbenzylidene)cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 154 mg (62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.35 (s, 1H), 7.87-7.82 (m, 2H), 7.66-7.64 (m, 2H), 3.28-3.20 (m, 1H), 1.86-1.29 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 157.2, 139.9, 132.1 (q, *J* = 33 Hz), 128.4, 125.6 (q, *J* = 4 Hz), 124.1 (q, *J* = 270 Hz), 70.2, 34.4, 25.7, 24.8. MS: *m/z* = 248 $[M-H]^+$. NMR data are in accordance with literature values.[186]



***N*-(4-Fluorobenzylidene)-cyclohexylamine**

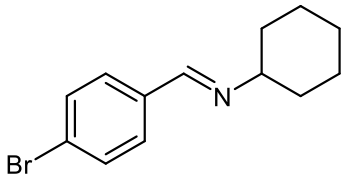
Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 150 mg (73%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 (s, 1H), 7.72 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 3.22-3.14 (m, 1H), 1.84-1.24 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 165.5 (d, *J* = 253 Hz), 157.3, 133.0, 130.1 (d, *J* = 10 Hz), 115.8 (d, *J* = 20 Hz) 70.0, 34.5, 25.8, 24.9. MS: *m/z* = 205 $[M]^+$. NMR data are in accordance with literature values.[94]



***N*-(4-Chlorobenzylidene)-cyclohexylamine**

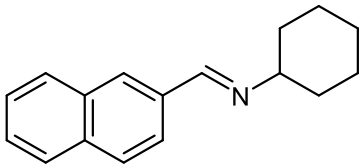
Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 186 mg (85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 3.23-3.16 (m, 1H), 1.85-1.24 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ

ppm: 157.4, 136.4, 135.2, 129.4, 128.9, 70.1, 34.4, 25.8, 24.9. MS: *m/z* = 222 $[M]^+$. NMR data are in accordance with literature values.[51]



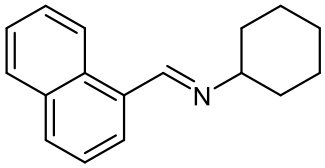
***N*-(4-Bromobenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a pale yellow solid. Yield: 162 mg (61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.25 (s, 1H), 7.64-7.46 (m, 4H), 3.22-3.15 (m, 1H), 1.83-1.24 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 157.4, 135.6, 131.8, 129.6, 124.7, 70.1, 34.4, 25.7, 24.9. MS: *m/z* = 265 $[M]^+$. NMR data are in accordance with literature values.[102]



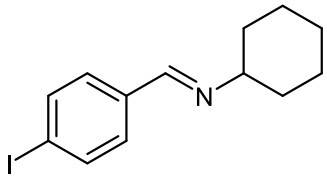
***N*-(2-Naphthalenylmethylene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 168 mg (71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.47 (s, 1H), 8.04-7.99 (m, 2H), 7.90-7.83 (m, 3H), 7.55-7.44 (m, 2H), 3.30-3.23 (m, 1H), 1.88-1.63 (m, 7H), 1.46-1.25 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.7, 134.6, 134.2, 133.1, 129.5, 128.6, 128.4, 127.8, 126.9, 126.4, 124.1, 70.1, 34.4, 25.7, 24.9. MS: *m/z* = 237 $[M]^+$. NMR data are in accordance with literature values.[187]



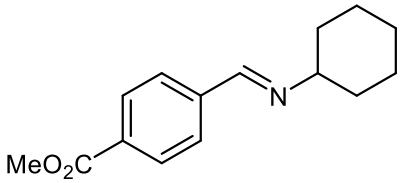
***N*-(1-Naphthalenylmethylene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 142 mg (60%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 9.00 (s, 1H), 8.91 (d, *J* = 8.4 Hz, 1H), 7.93-7.86 (m, 3H), 7.63-7.49 (m, 3H), 3.36-3.29 (m, 1H), 1.95-1.66 (m, 7H), 1.50-1.30 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.0, 133.9, 132.2, 131.4, 130.7, 128.7, 128.4, 127.0, 126.0, 125.4, 124.4, 71.0, 34.7, 25.8, 24.9. MS: *m/z* = 237 $[M]^+$. NMR data are in accordance with literature values.[187]



***N*-(4-Iodobenzylidene)-cyclohexylamine**

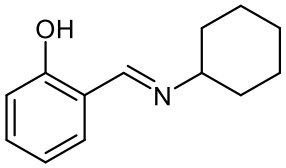
Following the general procedure for imine synthesis, the imine was isolated as a white solid. Yield: 191 mg (61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.23 (s, 1H), 7.74 (d, *J* = 8.3, 2H), 7.46 (d, *J* = 8.4, 2H), 3.23-3.15 (m, 1H), 1.85-1.22 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 157.7, 137.8, 136.2, 130.9, 129.8, 70.1, 34.4, 25.7, 24.9. GC-MS (EI, Pos): RT = 14.9 min, *m/z* = 313 $[M]^+$. NMR data are in accordance with literature values.[183]



***N*-(4-Carbomethoxybenzylidene)-cyclohexylamine**

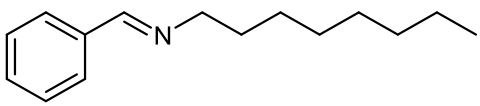
Following the general procedure for imine synthesis, the imine was isolated as a white solid. Yield: 20 mg (8%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.35 (s, 1H), 8.06 (d, *J* = 8.1, 2H), 7.79 (d, *J* = 8.0, 2H), 3.93 (s, 3H), 3.27-3.20 (m, 1H), 1.84-1.22 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ

ppm: 166.9, 157.8, 140.6, 131.7, 129.9, 128.1, 70.2, 52.4, 34.4, 25.7, 24.9. GC-MS (EI, Pos): RT = 15.0 min, *m/z* = 245 $[M]^+$. NMR data are in accordance with literature values.[185]



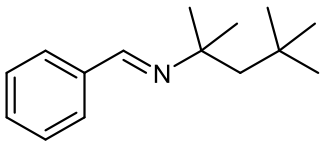
***N*-(2-Hydroxybenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the imine was isolated as a yellow liquid. Yield: 35 mg (17%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.36 (s, 1H), 7.23-7.21 (m, 2H), 6.95 (dd, *J* = 8.3 Hz, 1.1 Hz, 1H), 6.86 (td, *J* = 7.5, 1.1 Hz, 1H), 3.28-3.21 (m, 1H), 1.86-1.26 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 162.3, 161.6, 132.1, 131.2, 119.0, 118.5, 117.2, 67.6, 34.4, 25.6, 24.5. GC-MS (EI, Pos): RT = 13.7 min, *m/z* = 203 $[M]^+$. NMR data are in accordance with literature values.[187]



***N*-Benzylidene-octylamine**

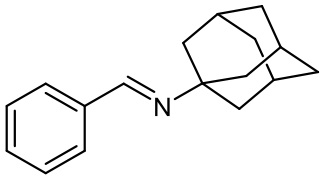
Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 195 mg (90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 (s, 1H), 7.78-7.68 (m, 2H), 7.42-7.39 (m, 3H), 3.61 (td, *J* = 7.1, 1.4 Hz, 2H), 1.72-1.68 (m, 2H), 1.37-1.27 (m, 10H), 0.91-0.82 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 160.8, 136.5, 130.6, 128.7, 128.1, 62.0, 32.0, 31.1, 29.6, 29.4, 27.5, 22.8, 14.3. MS: *m/z* = 216 $[M-H]^+$. NMR data are in accordance with literature values.[66]



***N*-Benzylidene-*tert*-octylamine**

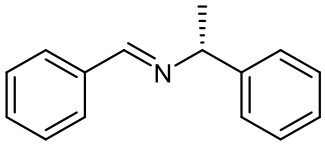
Following the general procedure for imine synthesis, the product was isolated as a clear liquid.

Yield: 139 mg (69%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.25 (s, 1H), 7.83-7.68 (m, 2H), 7.44-7.38 (m, 3H), 1.71 (s, 2H), 1.34 (s, 6H), 0.97 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 154.6, 137.5, 130.1, 128.7, 128.1, 61.2, 56.7, 32.2, 32.0, 29.8. MS: *m/z* = 216 $[M-H]^+$. NMR data are in accordance with literature values.[188]



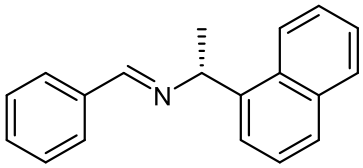
_N_-Benzylidene-1-adamantanylamine

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 210 mg (88%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.29 (s, 1H), 7.77 (bs, 2H), 7.48-7.34 (m, 3H), 2.18 (s, 3H), 1.84 (s, 6H), 1.74 (m, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 155.1, 137.2, 130.3, 128.6, 128.0, 57.6, 43.2, 36.7, 29.7. MS: *m/z* = 239 $[M]^+$. NMR data are in accordance with literature values.[189]



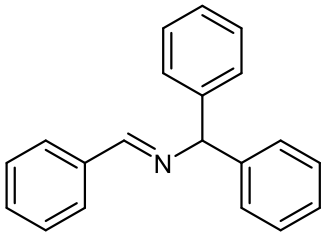
(_R_)-_N_-Benzylidene-1-phenylethylamine

Following the general procedure for imine synthesis, the product was isolated as a clear liquid. Yield: 138 mg (66%). $[\alpha]_D^{20}$ = -68.2 (*c* = 1.58, $CHCl_3$) (ref.[190] $[\alpha]_D^{27}$ = -64.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.26 (s, 1H), 7.70-7.67 (m, 2H), 7.40-7.06 (m, 8H), 4.44 (q, *J* = 6.6 Hz, 1H), 1.50 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 159.5, 145.3, 136.5, 130.6, 128.6, 128.5, 128.3, 126.9, 126.7, 69.8, 25.0. MS: *m/z* = 209 $[M]^+$. NMR data are in accordance with literature values.[190]



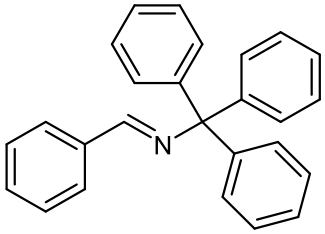
(*R*)-*N*-Benzylidene-1-(1-naphthyl)ethylamine

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 215 mg (83%). $[\alpha]_D^{20}$ = -232.6 (*c* = 1.00, $CHCl_3$) (ref.[190] $[\alpha]_D^{27}$ = -250.3 (c = 1.04, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.45 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.92-7.74 (m, 5H), 7.60-7.38 (m, 6H), 5.38 (q, *J* = 6.6 Hz, 1H), 1.76 (d, *J* = 6.6 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 159.8, 141.3, 136.6, 134.1, 130.8, 130.7, 129.1, 128.7, 128.4, 127.5, 125.9, 125.8, 125.4, 124.2, 123.8, 65.7, 24.7. MS: *m/z* = 259 $[M]^+$. NMR data are in accordance with literature values.[190]



***N*-Benzylidene-1,1-diphenylmethylamine**

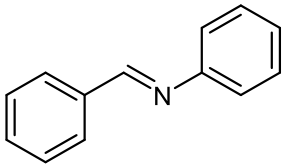
Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 198 mg (73%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.35 (s, 1H), 7.82-7.67 (m, 2H), 7.36-7.29 (m, 7H), 7.26-7.22 (m, 4H), 7.18-7.13 (m, 2H), 5.52 (s, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 160.9, 144.0, 136.5, 130.9, 128.7, 128.6, 128.6, 127.8, 127.1, 78.0. MS: *m/z* = 271 $[M]^+$. NMR data are in accordance with literature values.[191]



***N*-Benzylidene-1,1,1-triphenylmethylamine**

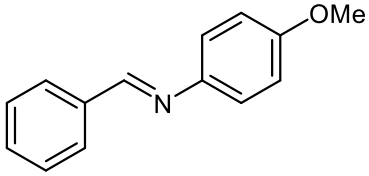
Following the general procedure for imine synthesis, the product was isolated as a white solid.

Yield: 66 mg (19%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.80-7.73 (m, 2H), 7.36-7.33 (m, 2H), 7.26-7.10 (m, 17H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 159.8, 146.0, 136.9, 130.9, 129.9, 128.7, 128.7, 127.9, 126.9, 78.4. MS: *m/z* = 347 $[M]^+$. NMR data are in accordance with literature values.[54]



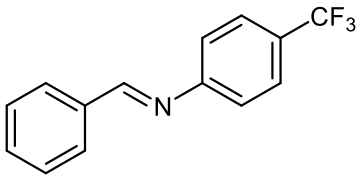
***N*-Benzylideneaniline**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 134 mg (74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.38 (s, 1H), 7.86-7.82 (m, 2H), 7.42-7.38 (m, 3H), 7.34-7.30 (m, 2H), 7.18-7.12 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 160.6, 131.6, 129.9, 129.3, 129.1 129.0, 128.9, 126.1, 121.0. MS: *m/z* = 187 $[M]^+$. NMR data are in accordance with literature values.[192]



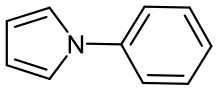
***N*-Benzylidene-*p*-anisidine**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 133 mg (63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.40 (s, 1H), 7.84-7.78 (m, 2H), 7.41-7.35 (m, 3H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.6, 158.4, 145.0, 136.5, 131.2, 128.9, 128.7, 122.3, 114.5, 55.6. MS: *m/z* = 211 $[M]^+$. NMR data are in accordance with literature values.[192]



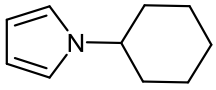
***N*-Benzylidene-4-(trifluoromethyl)aniline**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 154 mg (62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.44 (s, 1H), 7.94-7.92 (m, 2H), 7.66-7.64 (m, 2H), 7.54-7.48 (m, 3H), 7.28-7.26 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 162.2, 155.2, 135.7, 132.2, 129.3, 129.1, 127.8 (q, J = 33 Hz), 126.5 (q, J = 4 Hz), 125.8 (q, J = 270 Hz), 121.1. MS: *m/z* = 248 $[M-H]^+$. NMR data are in accordance with literature values.[193]



1-Phenylpyrrole

Following the general procedure for pyrrole synthesis, the product was isolated as a white solid. Yield: 67 mg (47%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.49-7.43 (m, 4H), 7.31-7.27 (m, 1H), 7.14 (t, J = 2.2 Hz, 2H), 6.40 (t, J = 2.2 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 140.9, 129.7, 125.7, 120.7, 119.4, 110.5. MS: *m/z* = 143 $[M]^+$. NMR data are in accordance with literature values.[194]



1-Cyclohexylpyrrole

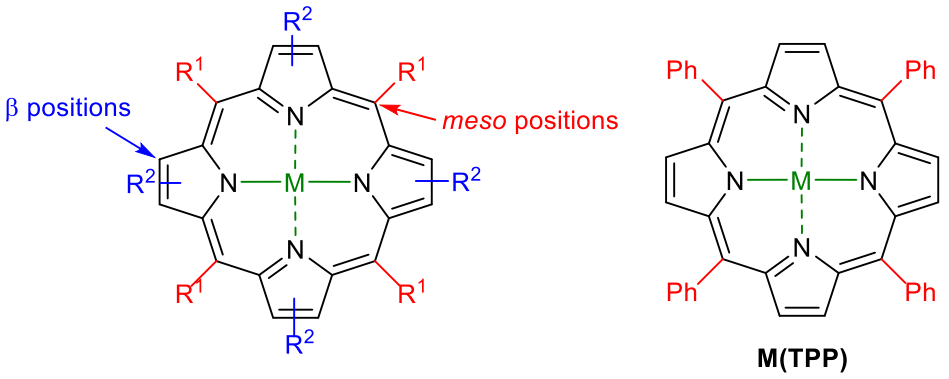
Following the general procedure for pyrrole synthesis, the product was isolated as a yellow liquid. Yield: 92 mg (62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 6.76 (t, J = 2.1 Hz, 2H), 6.16 (t, J = 2.2 Hz, 2H), 3.87-3.79 (m, 1H), 2.15-2.10 (m, 2H), 1.93-1.88 (m, 2H), 1.79-1.19 (m, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 118.4, 107.5, 58.8, 34.8, 25.9, 25.5. MS: *m/z* = 149 $[M]^+$. NMR data are in accordance with literature values.[156]

5. Vanadium(IV) porphyrin-catalyzed dehydrogenative coupling of primary alcohols and amines into imines

5.1 Background

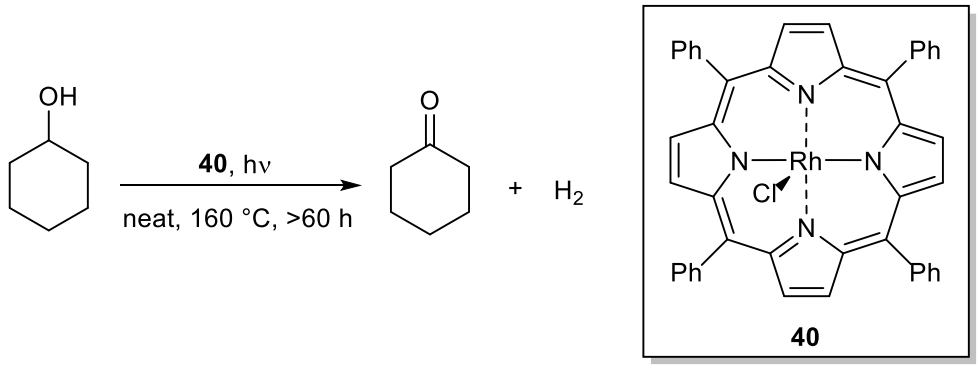
5.1.1 Metalloporphyrin-catalyzed AAD reactions

Metalloporphyrin derivatives are naturally occurring macrocyclic compounds, which play key roles in several life processes. Among others Heme B, Chlorophyll a and Cyanocobalamin are natural porphyrin-based complexes. Metalloporphyrins are well known for their applications in conductive materials, medicine, optics, magnetism, solar energy conversion and lately, the development of metalloporphyrins as catalysts in organic synthesis has evolved considerably.[195,196] The simplest metalloporphyrins with no substituents at the *meso* positions are rarely used as catalysts, since they easily undergo oxidative degradation.[197] To circumvent this problem, over time different substituents have been introduced at the *meso* positions as well as at the β-positions (Scheme **5.1**). The most common porphyrin derivative is the tetraphenylporphyrin (TPP), which has aryl moieties at the *meso* positions.



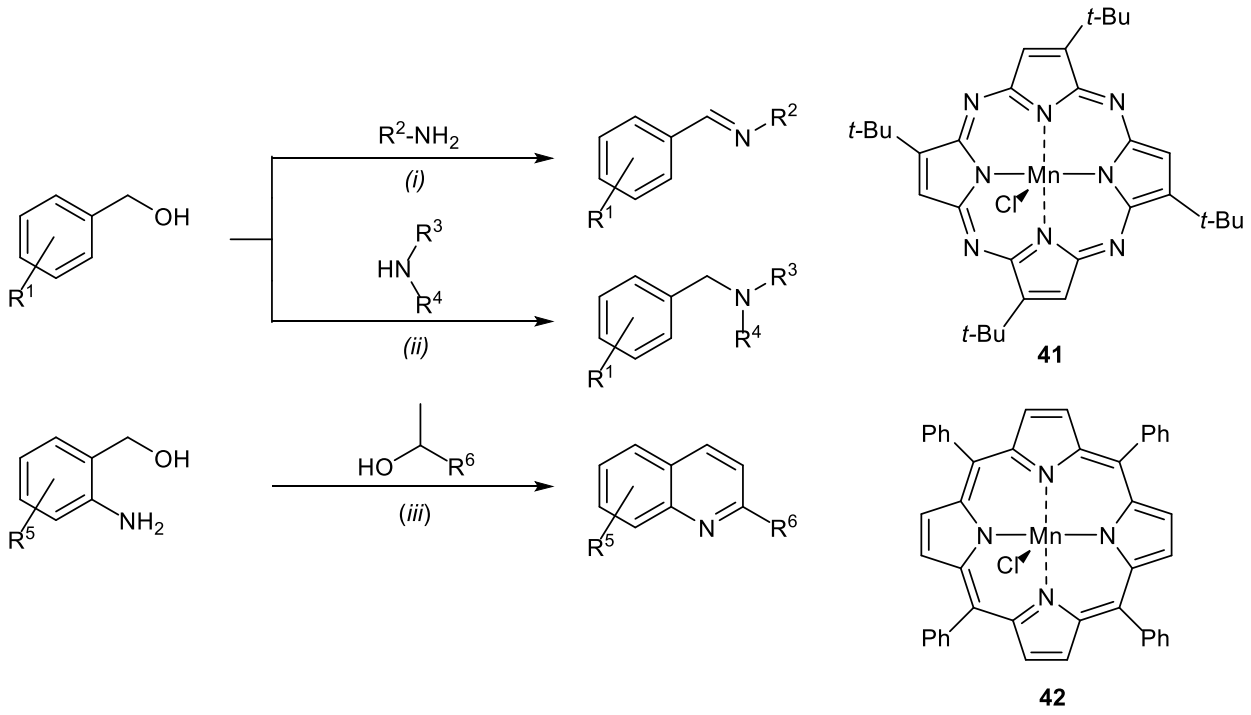
Scheme 5.1. Structure of general metalloporphyrin (left) and M(TPP) (right). M = metal.

Metalloporphyrins based on different metals have been used to catalyze several organic tranformations, including epoxidations,[198] sulfoxidations,[199] hydroxylations[200] and carbonylations,[201] although, most commonly in the presence of an oxidant. However, metalloporphyrins have also been used as catalysts in AAD reactions. One of the very first examples was published by Yasukazu Saito and coworkers in 1983,[202] who demonstrated that the photocatalyst Rh(TPP)Cl (**40)** could dehydrogenate both cyclohexanol and isopropanol into the corresponding carbonyl compounds (Scheme **5.2**).



Scheme 5.2. Photocatalytic acceptorless dehydrogenation of cyclohexanol catalyzed by **40**.

In 2019, the Madsen group reported the development of manganese(III) porphyrin chloride complexes as catalysts for AD coupling reactions of alcohols and amines.[203] The reaction has been used for the synthesis of imines, tertiary amines and quinolines using complex **41** and **42** as catalysts (Scheme **5.3**). The mechanism for these transformations is assumed to include the initial formation of a manganese(III) alkoxide species, which is believed to undergo degradation into the aldehyde and a manganese(III) hydride complex. Subsequently, the alkoxide complex is regenerated by reaction with another alcohol molecule, completing the catalytic cycle. The main drawback of these transformations is that the reactions are running in mesitylene. Hence, high temperatures are needed for the reactions to proceed.



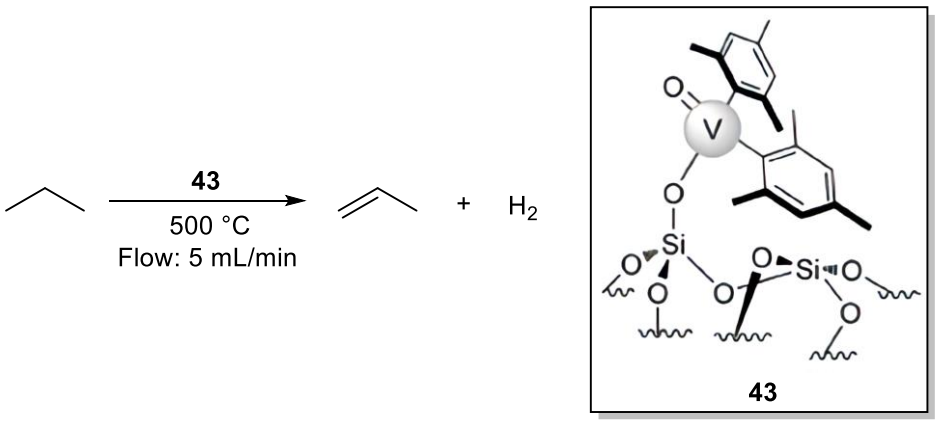
Scheme 5.3. Manganese porphyrin complexes used in different alcohol dehydrogenation reactions. *Reagents and conditions: (i)* 2 mol% **41**, 4Å MS, mesitylene, 164 ºC, 48 h. (*ii*) 3 mol% **41**, 20% K_2CO_3, 4Å MS, mesitylene, 164 ºC, 48 h. *(iii)* 5 mol% **42**, 20% pyridine, KOH, *t*-BuOK, 4Å MS, mesitylene, 164 ºC, 60 h.

Inspired by the manganese(III) porphyrin catalyzed dehydrogenative transformation of alcohols, speculations occured whether the manganese metal could be replaced with another Earth abundant metal while keeping the catalytic activity of the complex?

5.1.2 Vanadium as possible AAD catalyst

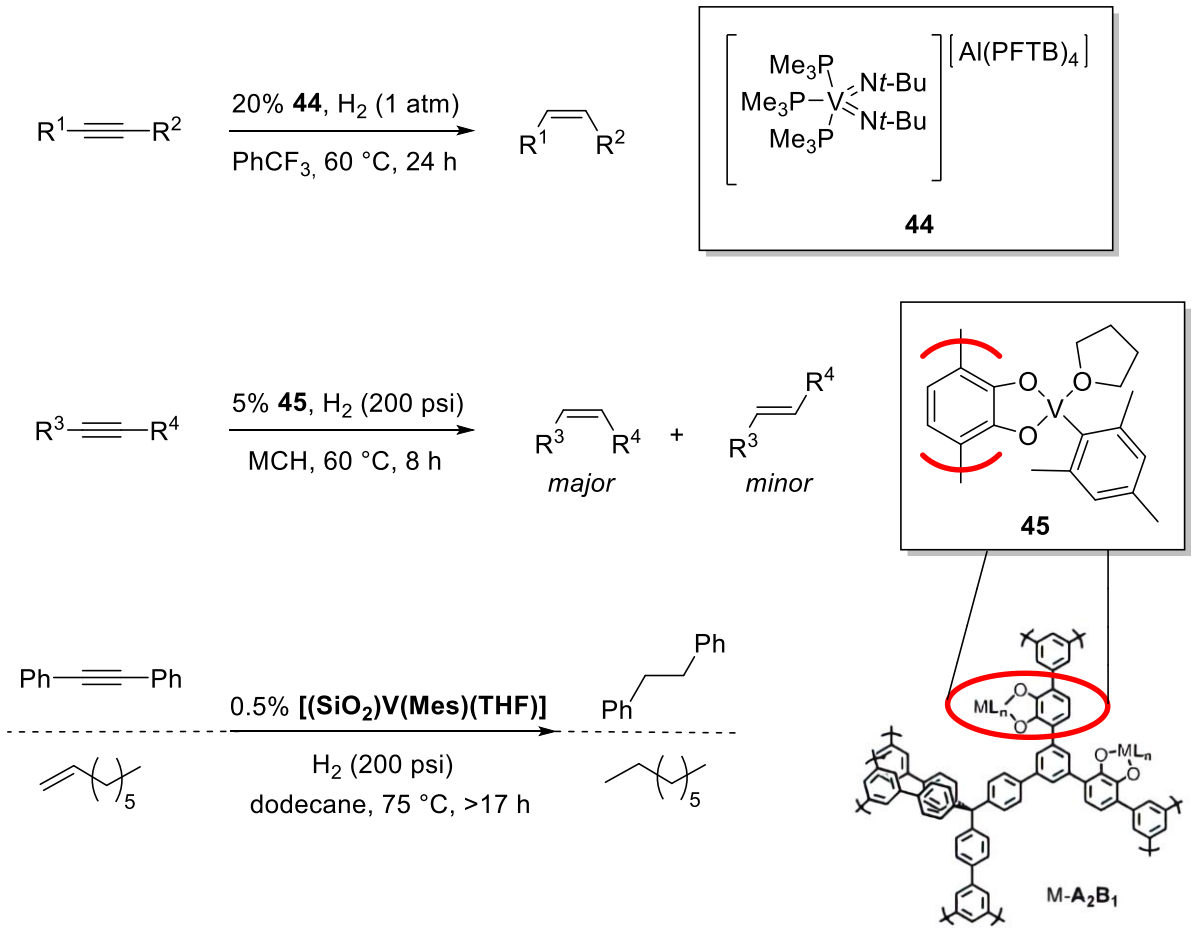
Vanadium is the sixth most abundant transition metal in the Earth's crust and the 20th most abundant among all elements.[204] Vanadium is a fairly cheap metal with a price around 40 €/kg and a worldwide production estimated to 79400 ton per year. Vanadium compounds in oxidation states ranging from - III to +V are known and thereby it encompasses both reductive and oxidative transformations in synthetic chemistry.[204] One of the key reactions that vanadium is known for is the modern sulfuric acid production, where V_2O_5 catalyzes the aerobic oxidation of sulfur dioxide to sulfur trioxide. This process was patented by Peregrine Phillips in 1831.[205] However, vanadium

compounds have been used as catalysts in a variety of organic reactions, including oxidations of alkanes, alkenes, arenes, sulfur compounds, alcohols and carbonyl groups, carbon-carbon and carbon-oxygen bond cleavage and formation, deoxydehydration, cyanation, ring-opening metathesis polymerization.[206,207] Additionally, vanadium has been used to catalyze the aerobic oxidative synthesis of imines from alcohols and amines, as mentioned in section **3.2** (Table **3.1**, entry 9).[69] On the other hand, limited attention has been drawn to the use of vanadium as catalyst in dehydrogenation reactions. Seemingly, the only examples involving vanadium-catalyzed non-oxidative dehydrogenation reactions include the dehydrogenation of light alkanes such as propane catalyzed by VO or $VO(Mes)_3$ supported on SiO_2, Al_2O_3 or TiO_2.[208–211] An example is shown in Scheme **5.4**.[211]



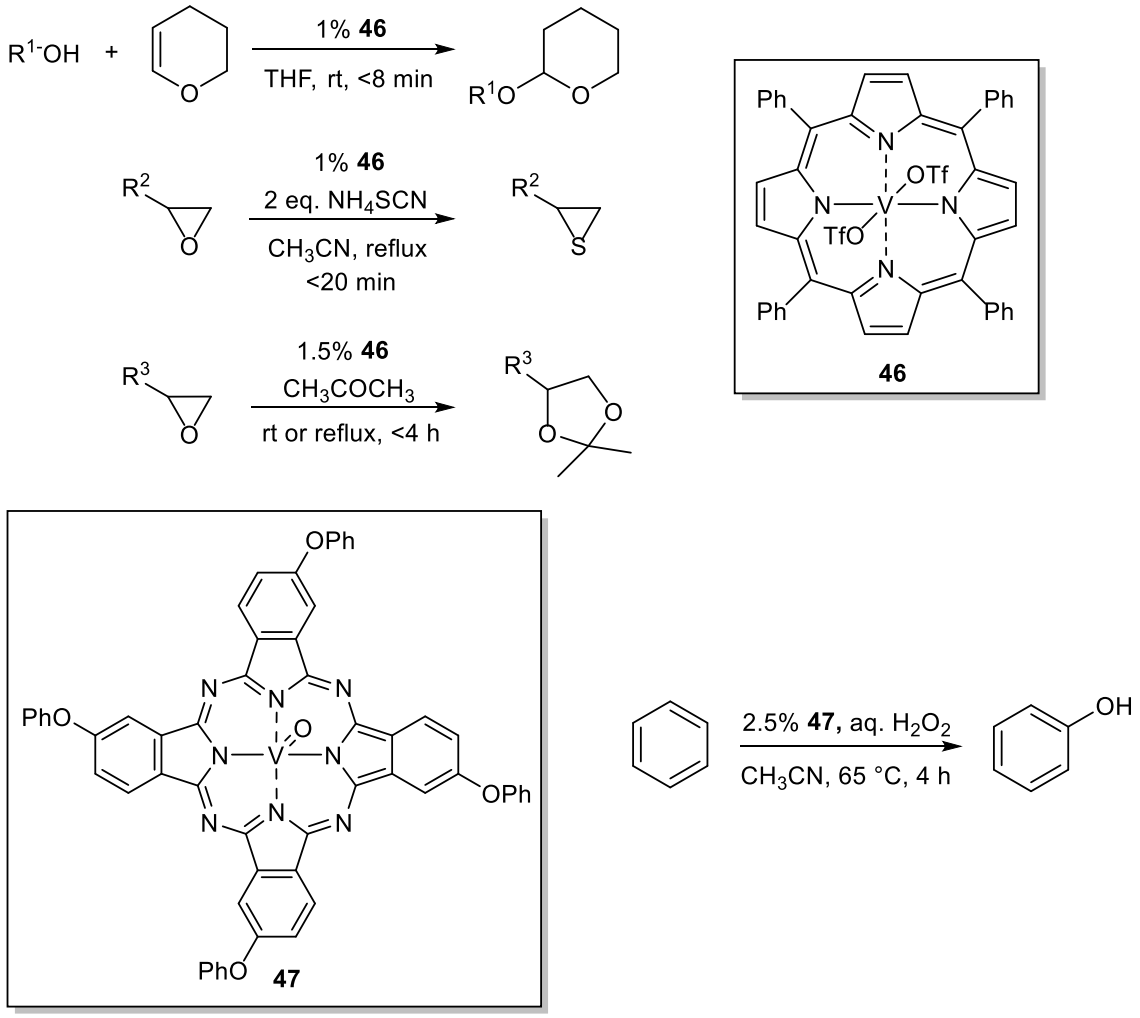
Scheme 5.4. Vanadium-catalyzed dehydrogenation of propane.

Conversely, more examples of vanadium-catalyzed hydrogenation reactions have been reported.[212–214] Different vanadium complexes, both supported and non-supported, have been shown able to catalyze the full or semihydrogenation of alkynes and alkenes under various conditions (Scheme **5.5**).



Scheme 5.5. Vanadium-catalyzed hydrogenation of alkynes and alkenes.

Vanadium(IV) compounds often exist as vanadyl derivatives with a VO^{2+} center. Consequently, most reported vanadium(IV) porphyrin complexes are oxovanadium compounds.[206,215] Nevertheless, also triflate vanadium(IV) porphyrin complexes have been used as catalysts in different reactions.[216–218] Some examples are shown in Scheme **5.6**.



Scheme 5.6. Vanadium(IV) porphyrin-catalyzed reactions.

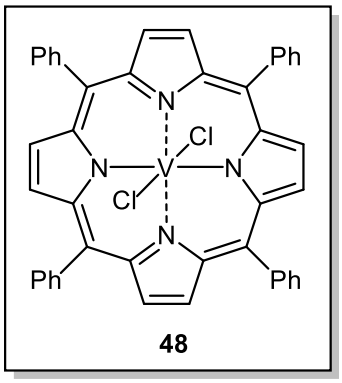
Also methods for preparing the corresponding extremely reactive dihalide vanadium(IV) porphyrin complexes have been developed.[219] However, the catalytic properties of these complexes have not been investigated to a full extent.

With all of the above in mind, the idea of investigating porphyrin vanadium(IV) dichloride complexes as catalysts in dehydrogenative transformations was encouraged, as a part of the search for new and more abundant metals to be used in the field of AD.

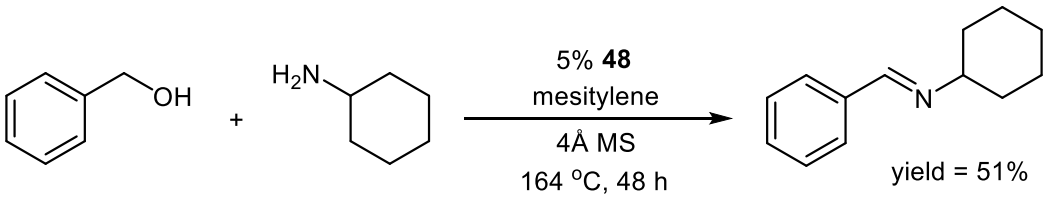
5.2 Results and discussion

5.2.1 Catalyst design and optimization of the reaction conditions

Initially, the commercially available tetraphenylporphine vanadium(IV) oxide complex was converted into the corresponding dichloride complex **48** with $SOCl_2$ and tested as catalyst for the standard dehydrogenative coupling reaction of benzyl alcohol and cyclohexylamine into the corresponding imine (Scheme **5.7**). When equimolar amounts of alcohol and amine was refluxed in mesitylene using 5% of complex **48** under a flow of N_2 for 48 hours, 51% of the imine product was obtained. This is not a breathtaking result, but it is indeed a good starting point.

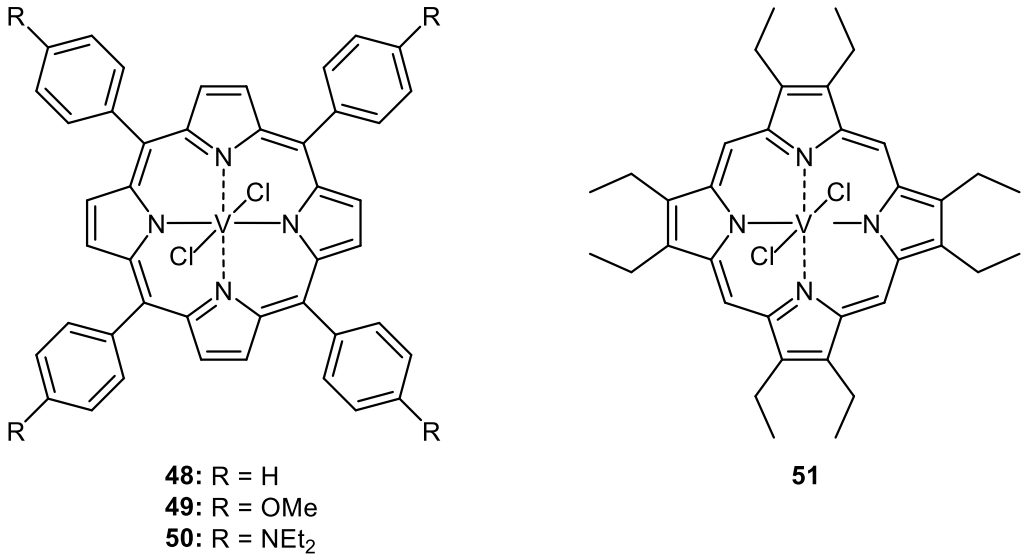


48



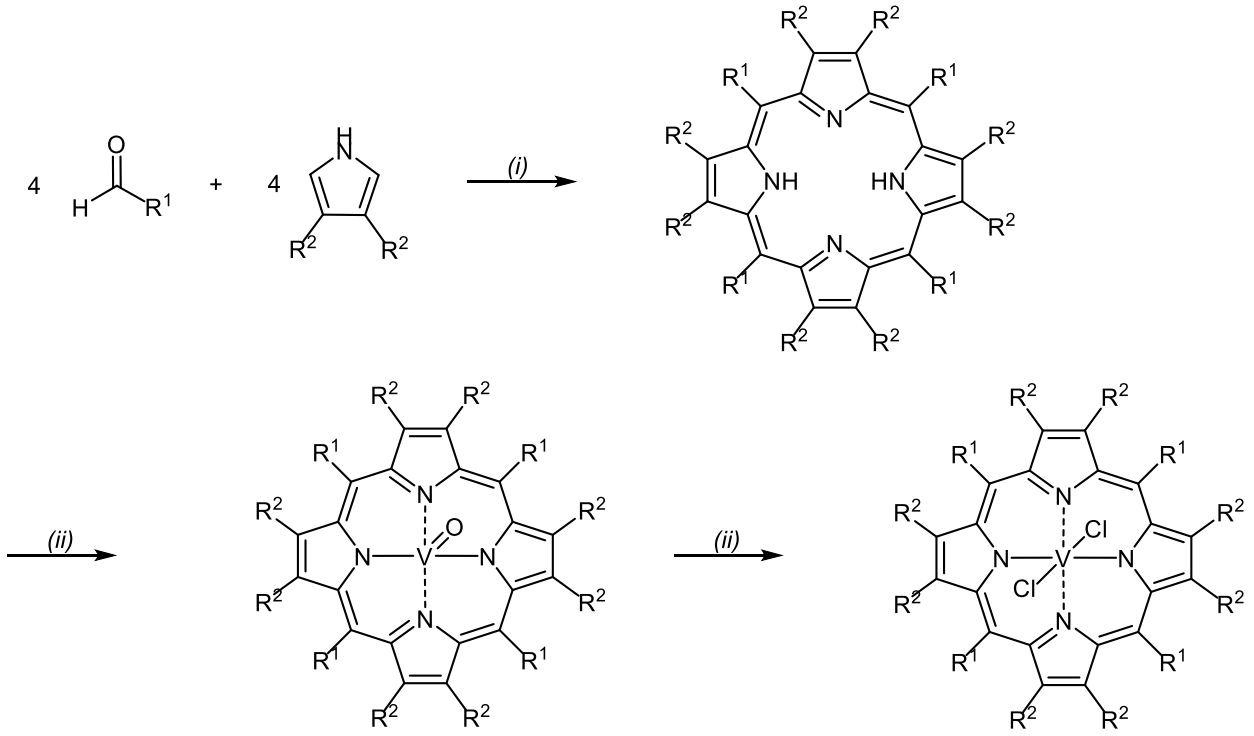
Scheme 5.7. Dehydrogenative imine synthesis catalyzed by vanadium(IV) porphyrin complex.

Afterwards, different vanadium(IV) porphyrin complexes were prepared to investigate the influence of substituents on the porphyrin scaffold (Scheme **5.8**). Only electron-donating groups were chosen as substituents on the tetradentate ligand, since only negative results have been obtained with electron-withdrawing groups previously in the Madsen group.[203]



Scheme 5.8. Vanadium(IV) complexes used for dehydrogenative imine synthesis.

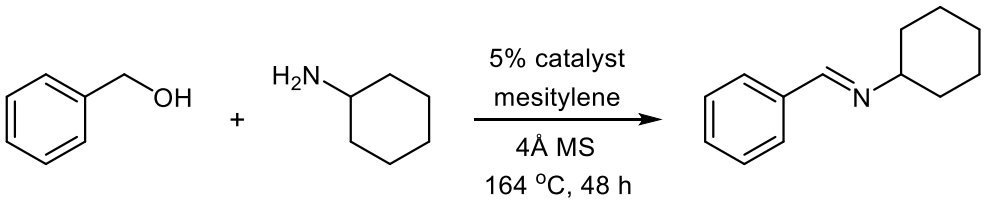
The complexes can be synthesized in three steps. First, the porphyrin ligands are prepared by a Rothemund condensation[220] of aldehydes with pyrroles. In contrast to the synthesis of the salen ligands, the purification of the porphyrin can be tedious and difficult. Next, oxovanadium(IV) complexes are obtained by mixing the ligand and VCl_3, which can be converted into desired dichloride complexes by treatment with $SOCl_2$ (Scheme **5.9**). Originally, the plan was to also test vanadium(IV) phthalocyanine complexes, but unfortunately, the conversion of the oxo-complexes into the dichloride complexes failed as reported previously.[219]



Scheme 5.9. Synthesis of different vanadium(IV) porphyrin complexes. *Reagents and conditions: (i)* propionic acid, reflux, 1 h *(ii)* VCl_3, DMF, reflux, 7 h. *(iii)* $SOCl_2$, degassed toluene, rt, 24 h.

For comparison, the synthesized complexes were studied as catalysts in the same reaction as complex **48** under the same conditions (Table **5.1**). Essentially the same result as with complex **48** (entry 1) was obtained with the methoxy-substituted (**49**) and octaethyl analogue (**51**) (entry 2 and 4), whereas the diaminoethyl-substituted analogue (**50**) gave considerably lower yield (entry 3). In the end, complex **48** was selected as catalyst for the dehydrogenative transformation, since it gave the highest yield and is the most easily available due to the fact that the corresponding oxovanadium(IV) complex is commercial.

Table **5.1**. Acceptorless alcohol dehydrogenation with vanadium(IV) porphyrin complexes.

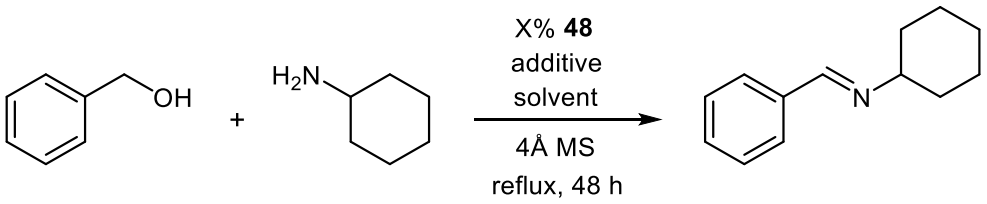


entry[a]	catalyst	imine yield (%)[b]
1	**48**	51
2	**49**	45
3	**50**	27
4	**51**	46

[a]Reaction conditions: BnOH (1 mmol), $CyNH_2$ (1 mmol), catalyst (0.05 mmol), tetradecane (0.5 mmol, internal standard), 4Å MS (150 mg), mesitylene (4 mL), reflux, 48 h. [b]Determined by GC.

For further optimization of the reaction, the influence of additives, solvent and concentration was investigated (Table **5.2**). Several additives were included in the reaction, but most of the additives led to lower or unchanged imine yields (entries 1-15). However, Li_3N, Cs_2CO_3 and NaOH had a positive effect on the transformation (entry 16, 21 and 26, respectively). With these three additives, the influence of the solvent and concentration was investigated. A significantly improved yield of 94% was observed when conducting the reaction in the presence of NaOH in a reduced amount of toluene (entry 31). This is an interesting result, since the previous experience in the Madsen group is that mesitylene is needed as solvent for the reaction to run using porphyrin-based complexes.[203] The optimum amount of NaOH was the original 20%, since both higher and lower quantities decreased the yield of the imine (entries 34 and 35). It was not possible to reduce the catalyst loading, since lowering the amount to 2.5% gave lower imine yield (entry 36). Additionally, it was not possible to remove the molecular sieves from the reaction, since a lower yield of the imine was then obtained. When complex **48** was removed from the reaction, only a minor amount of imine was formed (entry 37). In the end, 5% **48**, 20% NaOH and 4Å MS in refluxing toluene under a flow of nitrogen were chosen as the optimum conditions for the dehydrogenative coupling of equimolar amounts of alcohol and amine.

Table 5.2. Optimization of acceptorless alcohol dehydrogenation with complex **48.**



entry[a]	X	additive	Z	solvent	imine yield (%)[b]
1	5	LiCl	20	mesitylene (4 mL)	29
2	5	LiBr	20	mesitylene (4 mL)	0
3	5	LiF	20	mesitylene (4 mL)	35
4	5	$MgBr_2$	20	mesitylene (4 mL)	21
5	5	MgO	20	mesitylene (4 mL)	25
6	5	KOH	20	mesitylene (4 mL)	14
7	5	*t*-BuOK	20	mesitylene (4 mL)	34
8	5	Et_3N	20	mesitylene (4 mL)	30
9	5	K_3PO_4	20	mesitylene (4 mL)	32
10	5	K_2CO_3	20	mesitylene (4 mL)	25
11	5	Na_2SO_4	20	mesitylene (4 mL)	35
12	5	$MgSO_4$	20	mesitylene (4 mL)	41
13	5	Mg_3N_2	20	mesitylene (4 mL)	56
14	5	Ca_3N_2	20	mesitylene (4 mL)	24
15	5	LiOH	20	mesitylene (4 mL)	59
16	5	Li_3N	20	mesitylene (4 mL)	75
17	5	Li_3N	20	mesitylene (2 mL)	66
18	5	Li_3N	20	*o*-xylene (4 mL)	54
19	5	Li_3N	20	toluene (4 mL)	35
20	5	Li_3N	20	heptane (4 mL)	18
21	5	Cs_2CO_3	20	mesitylene (4 mL)	72
22	5	Cs_2CO_3	20	mesitylene (2 mL)	43
23	5	Cs_2CO_3	20	*o*-xylene (4 mL)	45
24	5	Cs_2CO_3	20	toluene (4 mL)	10
25	5	Cs_2CO_3	20	heptane (4 mL)	13
26	5	NaOH	20	mesitylene (4 mL)	68
27	5	NaOH	20	mesitylene (2 mL)	72
28	5	NaOH	20	mesitylene (1 mL)	66
29	5	NaOH	20	*o*-xylene (4 mL)	24

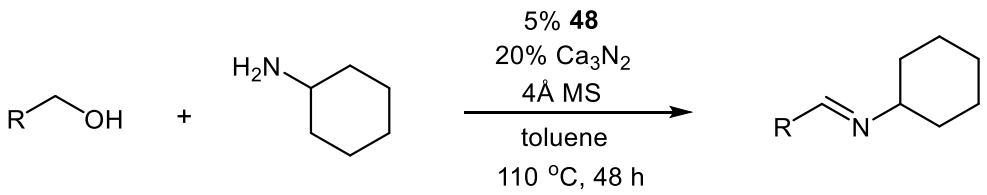
30	5	NaOH	20	toluene (4 mL)	69
31	5	NaOH	20	toluene (2 mL)	94
32	5	NaOH	20	toluene (1 mL)	69
33	5	NaOH	20	heptane (4 mL)	5
34	5	NaOH	30	toluene (2 mL)	70
35	5	NaOH	10	toluene (2 mL)	29
36	2.5	NaOH	20	toluene (2 mL)	67
37	-	NaOH	20	toluene (2 mL)	19

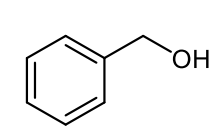
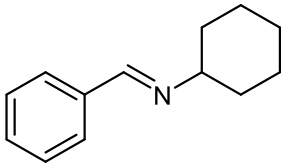
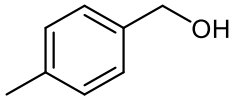
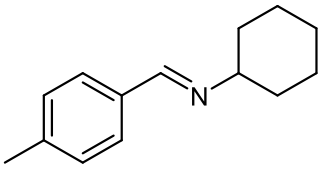
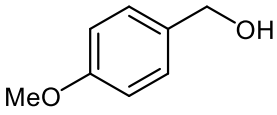
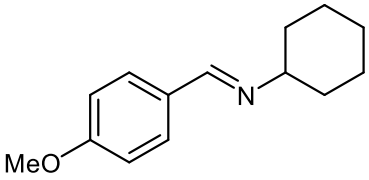
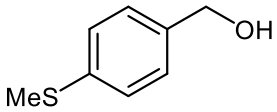
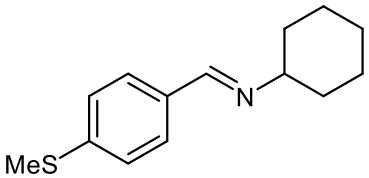
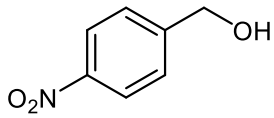
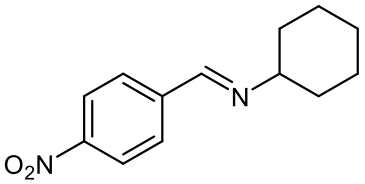
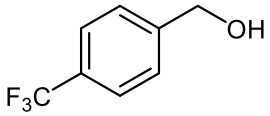
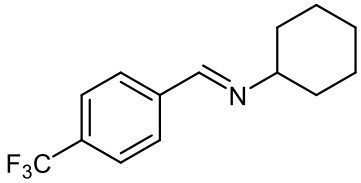
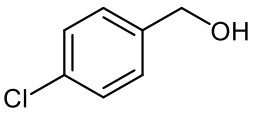
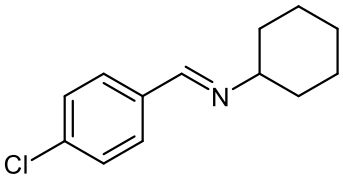
[a]Reaction conditions: BnOH (1 mmol), $CyNH_2$ (1 mmol), **48** (0.0X mmol), additive (0.Z mmol), tetradecane (0.5 mmol, internal standard), 4Å MS (150 mg), solvent, reflux, 48 h. [b]Determined by GC.

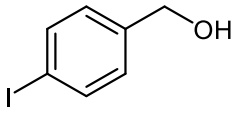
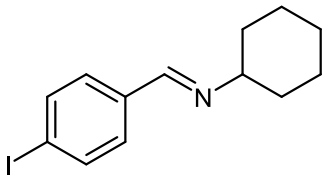
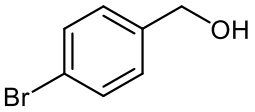
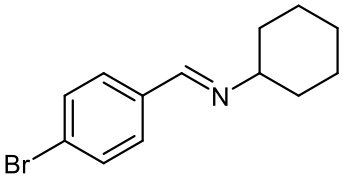
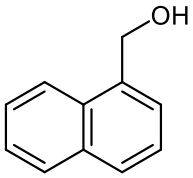
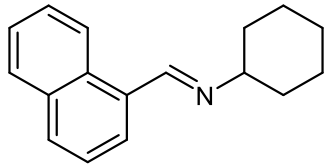
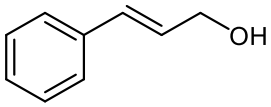
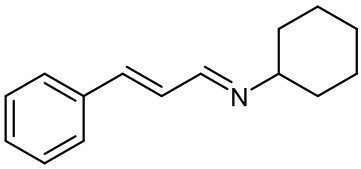
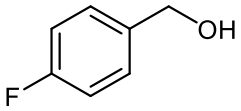
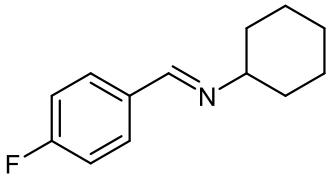
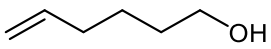
5.2.2 Substrate scope and limitations

The final conditions were applied to various alcohols and amines to investigate the substrate scope of this transformation. First, different alcohols were reacted with cyclohexylamine and the products were isolated by flash chromatography (Table **5.3**). This afforded 93% of the imine for the parent reaction with benzyl alcohol (entry 1). A *para*-substituent on the benzyl alcohol seems to have little influence on the imination reaction, since both electron-donating groups (such as methyl, methoxy and thiomethyl) and electron-withdrawing groups (such as nitro, trifluoromethyl and halides) furnished similar yields of the imines in the range of 65-94% (entries 2-9). 1-Napthalenemethanol afforded a yield of 84% of the corresponding imine (entry 10) and cinnamyl alcohol gave 82% yield (entry 11). No dehalogenation or reduction of neither nitro-group nor double bond was observed. For unknown reasons *p*-fluorobenzyl alcohol was a challenging substrate, yielding only 22% of the corresponding imine (entry 12). No by-products were observed, only poor conversion of the alcohol. Additionally, just as in the case of manganese(III) salen catalyst **19**, this transformation was not possible with aliphatic alcohols (entry 13).

Table 5.3. Imination of alcohols with cyclohexylamine catalyzed by complex **48**.



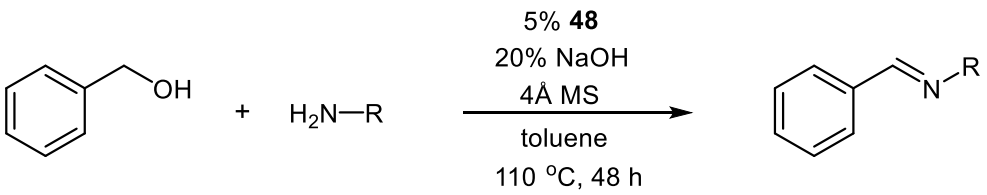
entry[a]	alcohol	imine	imine yield (%)[c]
1			93
2			65
3			82
4			78
5			94
6			77
7			70

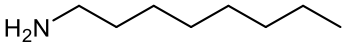
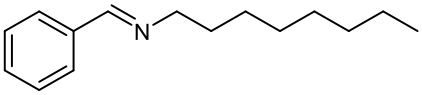
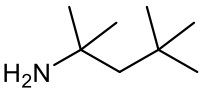
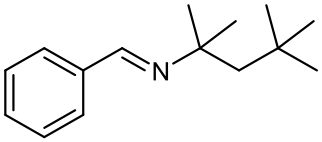
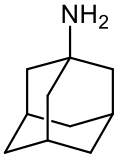
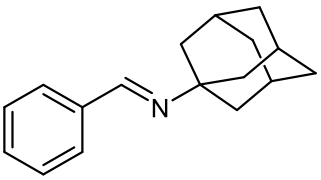
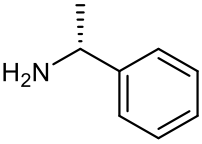
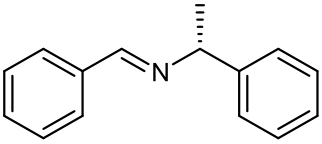
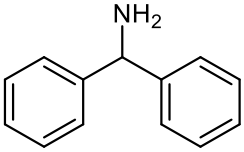
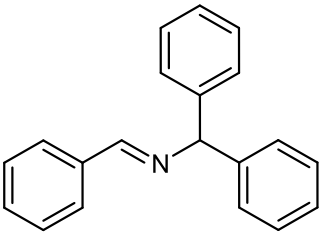
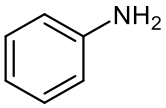
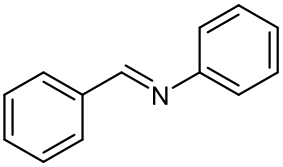
8			72
9			82
10			84
11			89
12			22
13		-	0

[a]Conditions: alcohol (1 mmol), $CyNH_2$ (1 mmol), **48** (0.05 mmol), NaOH (0.20 mmol), toluene (2 mL), reflux, 48 h. [b]Determined by GC-MS with tetradecane as internal standard. [c]Isolated yield.

In addition, different primary amines were reacted with benzyl alcohol (Table **5.4**). Octylamine furnished the imine product in 74% yield (entry 1) and benzhydrylamine gave the corresponding imine in 92% yield (entry 5). The more hindered amines 1-adamantylamine and *tert*-octylamine afforded the imines in moderate yields of 61 and 62%, respectively (entry 2 and 3). A similar yield was obtained with the optically pure amine (*R*)-1-phenylethylamine (entry 4) and no sign of racemization was observed. The transformation could be extended to arylamines to a certain degree, where aniline afforded 57% of the imine product (entry 6).

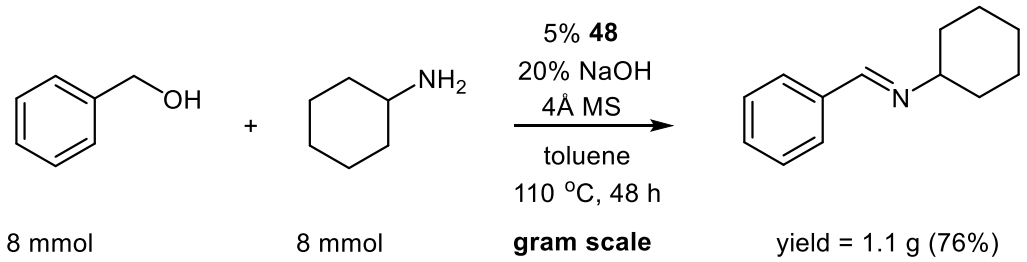
Table 5.4. Imination of alcohols with cyclohexylamine catalyzed by complex **48**.



entry[a]	amine	imine	imine yield (%)[c]
1			74
2			62
3			61
4			60
5			92
6			57

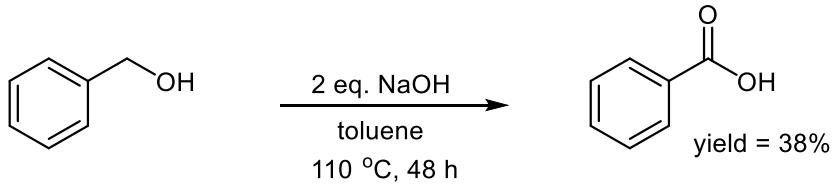
[a]Conditions: BnOH (1 mmol), amine (1 mmol), **48** (0.05 mmol), NaOH (0.20 mmol), toluene (2 mL), reflux, 48 h. [b]Determined by GC-MS with tetradecane as internal standard. [c]Isolated yield.

Furthermore, the dehydrogenative coupling of benzyl alcohol and cyclohexylamine could easily be scaled up to gram scale affording the corresponding imine in an acceptable yield (Scheme **5.10**). This is a very important feature, since acceptorless dehydrogenation is primarily interesting for working on an industrial scale to produce large amounts of hydrogen gas.



Scheme 5.10. Gram scale reaction of benzyl alcohol and cyclohexylamine.

In many cases, the conversion of the alcohol was significantly higher than the obtained yield of the imine, even though no by-products were observed by GC-MS. As the only discovered by-product, a small amount of a precipitate, assigned as benzoic acid, was often observed during the imine synthesis. To investigate the possibility for obtaining benzoic acid as the major product, two equivalents of NaOH was added to the reaction instead of the normal 20 mol%. In this case, the yield was increased to almost 40% of the acid. Unfortunately, it turned out to be a background reaction, since essentially the same yield was obtained after removing the catalyst from the reaction (Scheme **5.11**). However, as long as the amount of the base was kept at the original 20 mol%, this side reaction was not a major problem for the imine synthesis (Table **5.2**, entry 37), but it might explain some of the varying yields in the substrate scope.



Scheme 5.11. Background reaction: base-catalyzed synthesis of carboxylic acid.

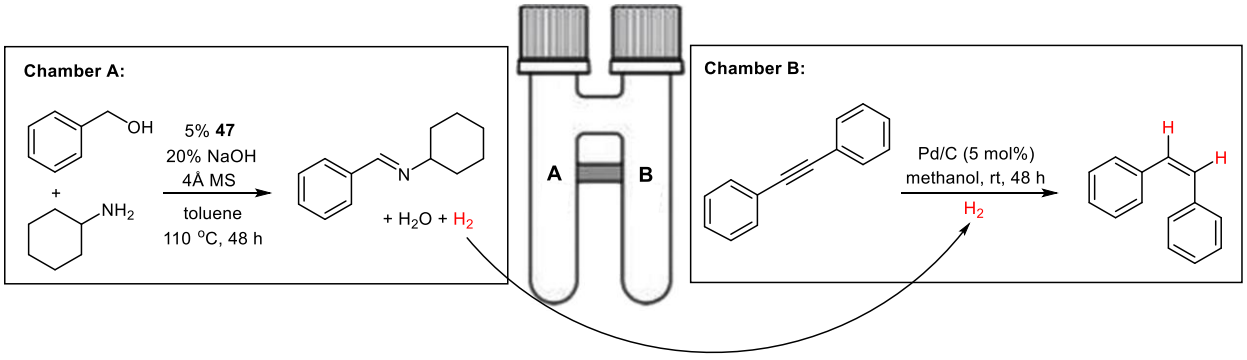
Just as the manganese(III) salen catalyst **19**, vanadium(IV) porphyrin complex **48** was tested in several other dehydrogenative reactions (appendix **A2**) and hydrogenation reactions (appendix **A1**). Unfortunately, all attempts led to no or poor conversion into the desired products.

5.2.3 Investigation of the reaction mechanism

Various experiments were carried out to explore the imination reaction mechanism using complex **48** as catalyst.

Hydrogen development

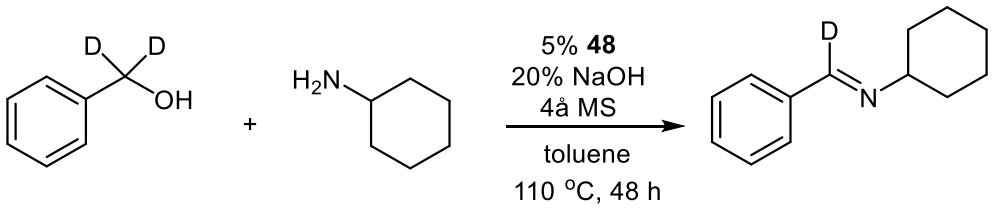
The dehydrogenative pathway of the imine formation was verified by performing the optimized imination reaction (Table **5.2**, entry 31) in a closed two-chamber system,[102,203,221] where diphenylacetylene and Pd/C in methanol was added to the second chamber. This experiment showed partial reduction of diphenylacetylene to *cis*-stilbene, confirming the evolution of hydrogen gas during the reaction (Scheme **5.12**).



Scheme 5.12. Produced hydrogen gas from dehydrogenative pathway in chamber A used in the reduction of diphenylacetylene in chamber B.

Deuterium scrambling, KIE and radical scavengers

When the optimized imination reaction in Table **5.2**, entry 31 was conducted with $PhCD_2OH$ instead of regular $PhCH_2OH$, the product formed was solely the corresponding deuterated imine PhCD=NCy with no traces of hydrogen incorporation into the benzylic position (Scheme **5.13**). This result is consistent with a monohydride pathway, since the identity of the α-hydrogens are maintained. Furthermore, no deuterium was incorporated into complex **48** as determined by LC-MS.



Scheme 5.13. Imination with benzyl alcohol α,α-d_2

Additionally, the primary KIE was measured. The initial rate was determined with both $PhCH_2OH$ and $PhCD_2OH$ in the reaction with cyclohexylamine (Figure **5.1**). This gave a KIE of 2.5, which shows that the C-H breakage might be one of several slow steps in the transformation.

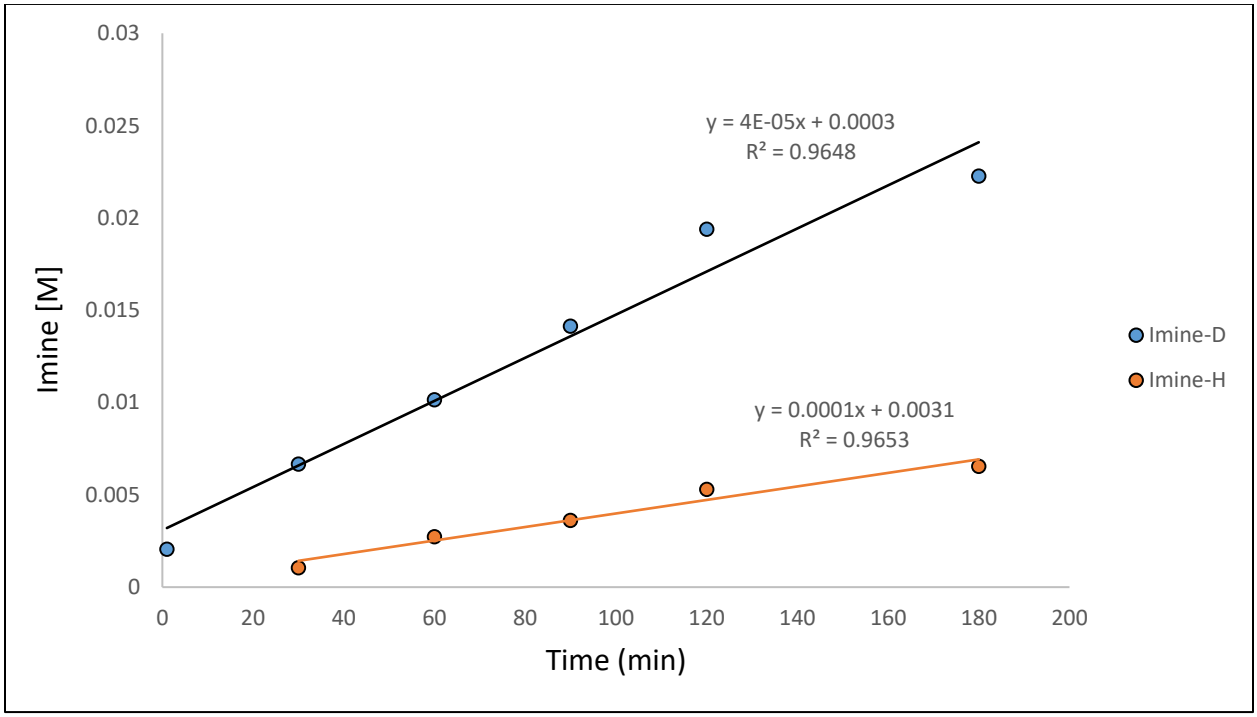
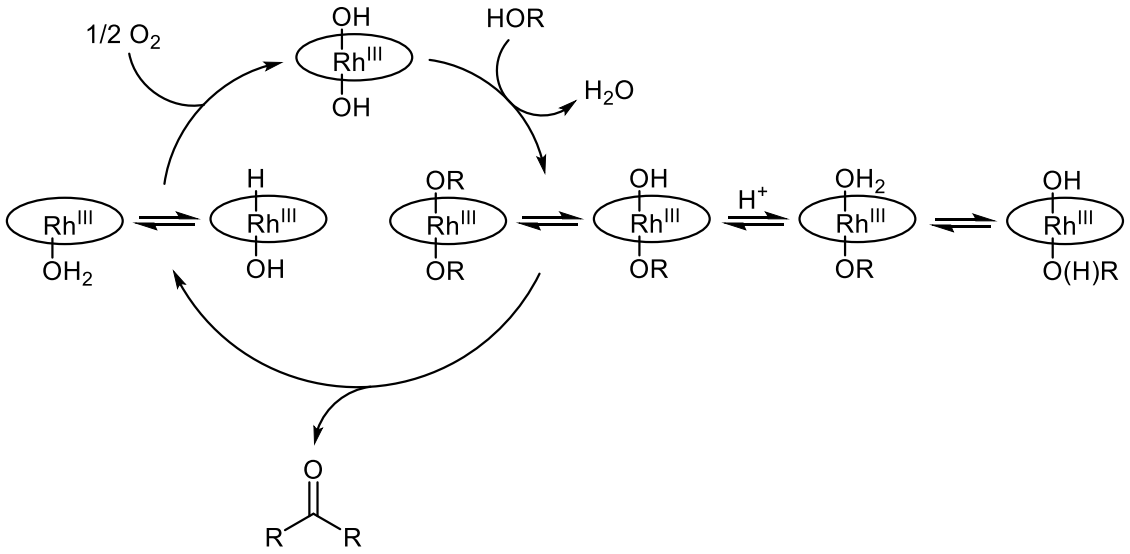


Figure 5.1. Determination of KIE by plotting the initial rates of the reactions involving benzyl alcohol and α,α-d_2-benzyl alcohol.

To investigate the possibility of the involvement of radical intermediates in the reaction mechanism, two separate experiments were carried out, where the optimized imination reaction (Table **5.2**, entry 31) was performed in the presence of one equivalent of two different radical scavengers; 2,4-diphenyl-4-methylpent-1-ene[166] and cyclohexa-1.4-diene.[165] In both cases, the radical trapping agents had no influence on the imine yield. Additionally, the two scavengers were not converted during the reactions according to GC-MS analysis. Based on these results, a radical mechanism most likely can be excluded.

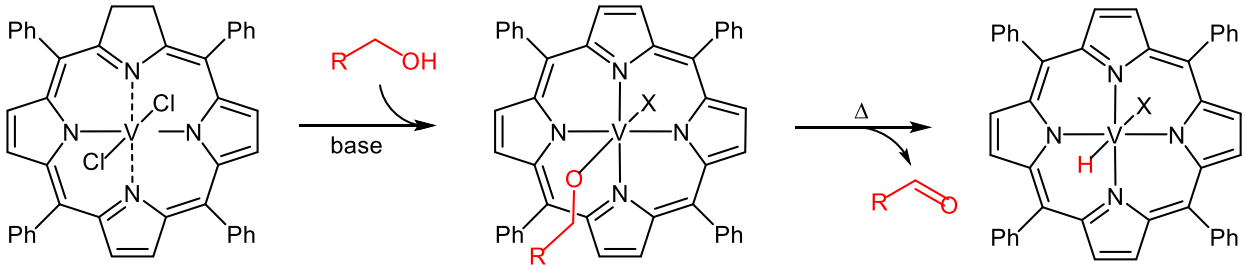
Identification of catalyst intermediate

No coordination site is available in catalyst **48** for a classical β-hydride elimination. Nevertheless, a rhodium(III) tetra(p-sulfonatophenyl) porphyrin (TSPP)Rh(III) complex, which is used as catalyst in aerobic oxidation of alcohols in water, has been shown to react with isopropanol to produce acetone and rhodium(III) hydride species in the absence of dioxygen,[222] although the exact reaction mechanism for this transformation is not known.[223] Furthermore, rhodium(III) porphyrin alkoxide species was directly observed. Based on these results, a mechanism was proposed in which the rate-determining step is Rh^{III}-alkoxide β-C-H elimination, which produces the ketone or aldehyde and (TSPP)Rh^{III}-H (Scheme **5.14**).



Scheme 5.14. Proposed mechanism for catalytic oxidation of alcohols in water mediated by (TSPP)Rh(III).

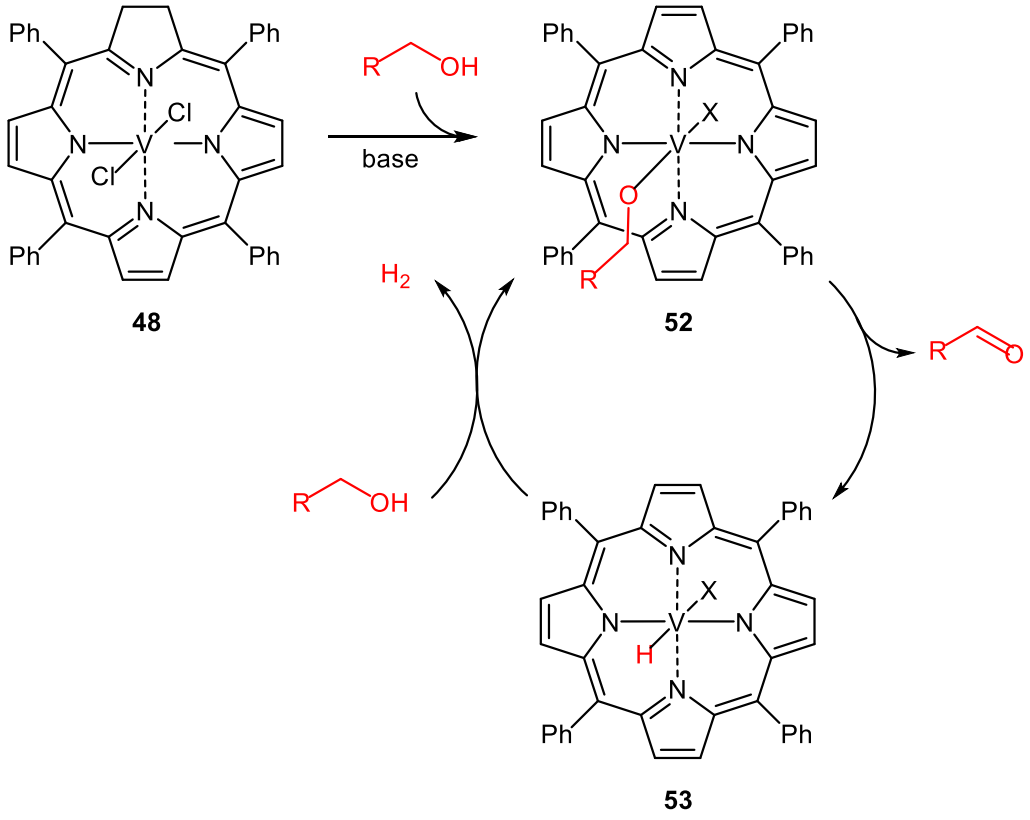
As mentioned in section **5.1**, the Madsen group has previously published dehydrogenative reactions performed by manganese(III) porphyrin complexes **41** and **42**.[203] The reaction mechanism for these transformations has been studied and involves the formation of a manganese(III) alkoxide complex degrading under the formation of the carbonyl product and manganese(III) hydride species. Due to the similarity of the complexes, it seems reasonable to believe that the mechanism with the vanadium(IV) porphyrin catalyst **48** is the same, even though vanadium porphyrin hydride species seemingly have never been characterized. To investigate this, an experiment was performed where complex **48** (1 mmol) was mixed with benzyl alcohol (50 mmol) and NaH (10 mmol). After stirring for 40 min at room temperature, LC-MS analysis of the mixture showed formation of the benzyloxy complex (TPP)V^{IV}(OBn). With a distillation head attached, the reaction mixture was then heated to 185 ºC for 16 h. A GC-MS analysis of the distillate showed that 2 mmol of a 11:1 mixture of benzyl alcohol and benzaldehyde was collected. This experiment shows that a vanadium(IV) alkoxide complex can undergo degradation with the formation of the aldehyde and presumably a vanadium(IV) hydride species (Scheme **5.15**).



Scheme 5.15. Investigation of possible formation of vanadium(IV) alkoxide species.

Possible reaction mechanism

Based on this result, we believe that the most probable mechanism is indeed the same as the one proposed for the manganese(III) porphyrin complexes **42** and **43**. Initially, the alkoxide complex **52** is formed, which is then converted into the aldehyde and hydride complex **53**. Consecutive reaction with the alcohol regenerates **52** and forms hydrogen gas (Scheme **5.16**).



Scheme 5.16. Proposed mechanism for vanadium(IV) catalyzed imine synthesis.

5.3 Project conclusion

In summary, a new vanadium(IV) porphyrin catalyst for the acceptorless dehydrogenation of alcohols has been developed. Complex **48** catalyzes the direct synthesis of imines from different alcohols and amines with the liberation of hydrogen gas. The catalytic cycle is believed to involve a porphyrin vanadium(IV) alkoxide species, which upon degradation gives rise to the formation of the aldehyde and supposedly the corresponding vanadium(IV) hydride complex. Subsequently, the alkoxide species is regenerated after reaction with the alcohol and liberation of hydrogen. This constitutes the first example of a vanadium catalyst for acceptorless dehydrogenation of alcohols and anaerobic direct synthesis of imines from alcohols and amines. Consequently, vanadium can be added to the list of base metals able to do acceptorless alcohol dehydrogenation.

5.4 Experimental section

5.4.1 General experimental methods

All commercial reagents were purchased from Sigma-Aldrich, Strem Chemicals, Fluorochem or abcr and used as received. NMR spectra were recorded at 400 MHz for ^{1}H-NMR and 101 MHz for ^{13}C-NMR on a Bruker Ascend 400 MHz spectrometer. Chemical shift values (δ) are reported in ppm relative to the residual solvent signal in $CDCl_3$ (δ_H 7.26 ppm, δ_C 77.2 ppm) while coupling constants (*J*) are given in Hz. High Resolution mass spectra were recorded using ESI with TOF detection. GCMS was carried out on a Shimadzu GCMS-QP2010S instrument fitted with an Equity 5, 30m×0.25mm×0.25μm column. Ionisation was performed by electronic impact (EI, 70eV) and helium as the carrier gas. LCMS was performed on a Waters ACQUITY UPLC system equipped with PDA and SQD2 electrospray MS detector. Column: Thermo accucore C18 (2.6 μm, 2.1 x 50 mm). Column temperature: 50 ºC. Flowrate 0.6 mL/min. Solvent A: 5 mM NH_4OAc in water, solvent B: 5 mM NH_4OAc in acetonitrile/water 95/5. Flash column chromatography was performed using silica gel 60 (0.035-0.070 mm particle size) saturated with Et_3N. Mesitylene was dried over molecular sieves (4 Å) while toluene was obtained by using a Pure Solv™ Micro solvent purification system. The water content of the solvents and liquid reagents was measured on a Karl-Fischer apparatus. All experiments were carried out under a nitrogen flow using Schlenk flask techniques except for the synthesis of the catalysts.

5.4.2 General procedure for imine synthesis

Vanadium complex **48** (36.7 mg, 0.05 mmol), NaOH (8.0 mg, 0.20 mmol) and pre-activated 4Å molecular sieves (150 mg) were placed in an oven-dried tube, whereafter it was placed in a Radley carousel. Vacuum was applied and the flask was then filled with nitrogen gas (repeated three times). Anhydrous toluene (2 mL) was added and the reaction mixture was heated to reflux. Alcohol (1 mmol), amine (1 mmol) and tetradecane (0.5 mmol as internal standard) were added by a syringe, and the reaction was refluxed with stirring under a flow of nitrogen for 48 h. The mixture was cooled to room temperature and the solvent removed in vacuo. The crude product was purified by silica gel column chromatography (hexane with 2% Et_3N) to afford the desired imine.

5.4.3 Gas development

To confirm the H_2 evolution, a two-chamber system was set up. Vanadium complex **48** (36.7 mg, 0.05 mmol), NaOH (8.0 mg, 0.20 mmol) and pre-activated 4Å molecular sieves (150 mg) were added in chamber one, while Pd/C (20 mg) and diphenylacetylene (0.1 mmol) were added in chamber two. The system was subjected to vacuum and refilled with N_2 gas three times. Then, freshly degassed toluene (2 mL) was added to chamber one and methanol (3 mL) was added to chamber two. Chamber one was then heated to reflux, while chamber two was kept at room temperature. After addition of benzyl alcohol (0.11 mL, 1.0 mmol) and cyclohexylamine (0.12 mL, 1.0 mmol) to chamber one, the system was closed completely. After 48 h, GC-MS showed that hydrogen gas released from the dehydrogenation reaction partly reduced diphenylacetylene to *cis*-stilbene.

5.4.5 Deuterium labelling study

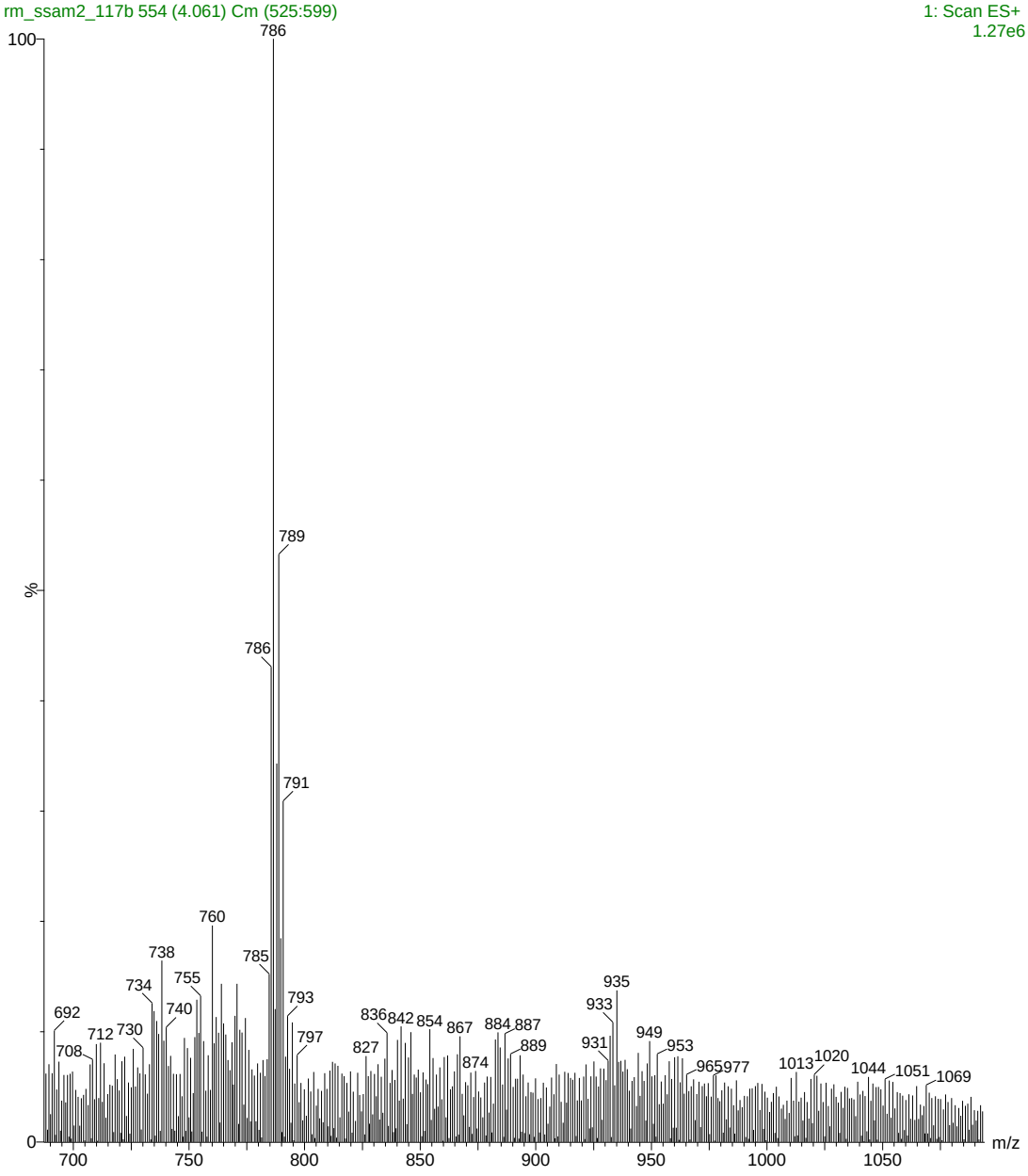
Benzyl alcohol-α,α-d_2 (110 mg, 1.0 mmol) and cyclohexylamine (99.0 mg, 1.0 mmol) were placed in an oven-dried tube and subjected to the imination reaction following the general procedure for imine synthesis. After purification of the product imine, examination of the ^{1}H-NMR revealed that the product imine was obtained as a pure deuterium-labeled imine and no hydrogen/deuterium scrambling had occurred.

5.4.6 Determination of deuterium isotope effect

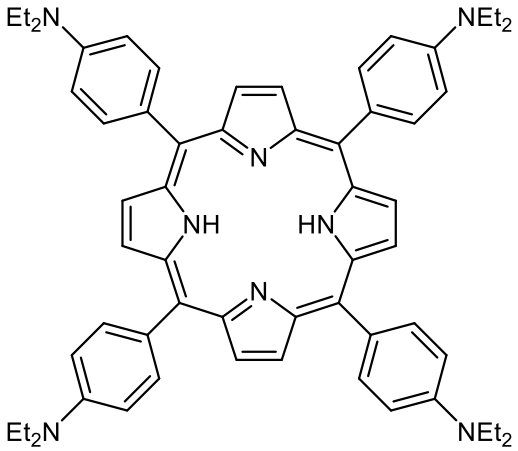
Benzyl alcohol (108 mg, 1.0 mmol) and cyclohexylamine (99 mg, 1.0 mmol) were placed in an oven-dried tube and subjected to the imination reaction following the general procedure for imine synthesis. For 5 h, a sample of 50 µL was taken out every 30 minutes, transferred to a GC vial, diluted to 1 mL with diethyl ether and then subjected to GCMS analysis to follow the formation of *N*-benzylidenecyclohexylamine and determine the initial rate (r). The same procedure was repeated using benzyl alcohol-α,α-d_2 (110 mg, 1.0 mmol) instead of non-deuterated benzyl alcohol. The initial rate for the transformation of benzyl alcohol was $r_H = 1.00\ 10^{-4}$ M/min. The initial rate for the reaction of benzyl alcohol-α,α-d_2 was $r_D = 4.00\ 10^{-5}$ M/min. The isotope effect was k_H/k_D = 2.50.

5.4.4 Identification of catalyst intermediate

A solution of Vanadium complex **48** (734 mg, 1 mmol) in benzyl alcohol (5 mL, 50 mmol) was treated portion wise with NaH (240 mg, 10 mmol) at room temperature under N_2. After 30 min at room temperature, LC-MS showed a peak corresponding to the benzyloxy complex (TPP)V(OBn) ($[M+H]^+$, 786 *m/z*). The mixture was then heated to 185 ºC with a distillation head attached under a N_2 atmosphere. After 16 h, 2 mmol of a 11:1 mixture of benzyl alcohol and benzaldehyde has been distilled of from the reaction.



5.4.7 Procedures for ligand synthesis



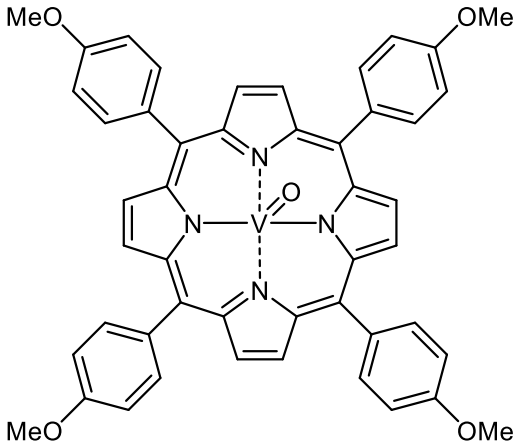
5,10,15,20-Tetra(4-diethylaminophenyl)-21*H*,23*H*-porphine

4-Diethylaminobenzaldehyde (1.1 g,7.3 mmol) and propionic acid (30 mL) was stirred at 138 ºC. Then freshly distilled pyrrole (0.5 mL 7.3 mmol) was added and the resulting solution was refluxed for 1 h. After cooling to room temperature, the reaction mixture is filtered and the filter cake is washed thoroughly with acetone. Purification by silica gel column chromatography (0-25% EtOAc/hexane) afforded 5,10,15,20-tetra(4-diethylaminophenyl)-21*H*,23*H*-porphine as a black solid. Yield: 1.3 g (20%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.94 (s, 8H), 8.08 (d, *J* = 8.8 Hz, 8H), 7.06 (d, *J* = 9.0 Hz, 8H), 3.71-3.61 (m, 16H), 1.47-1.30 (m, 24H), -2.52 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 146.8, 136.2, 129.5, 127.9, 120.6, 111.2, 110.1, 44.7, 13.0. NMR data are in accordance with literature values.[224]

5.4.8 Procedures for vanadium(IV) catalyst synthesis

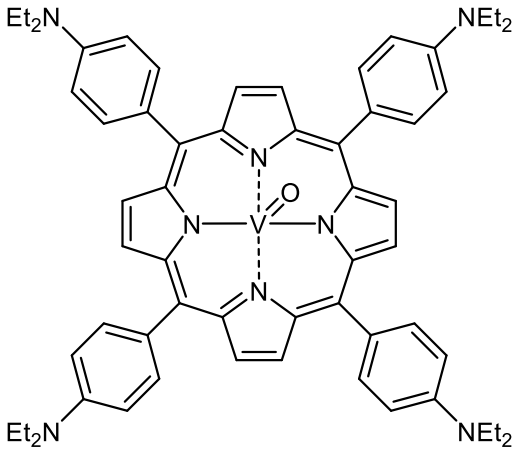
General procedure for synthesis of vanadium oxide complexes

Ligand (0.22 mmol) and VCl_3 (176 mg, 1.20 mmol) were refluxed in dimethylformamide (10 mL) for 7 hours. After evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL) and the mixture was washed with water (10 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The resulting crystals were washed with hexane and dried under vacuum.



5,10,15,20-Tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphine vanadium(IV) oxide

Following the general procedure for synthesis of vanadium dichloride complexes with 5,10,15,20-tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphine, the complex was obtained as dark purple crystals. Yield: 163 mg (93%). FTIR, ν/cm^{-1}: 2849 m, 1217 s, 1143 m, 1005 s, 760 w.[195]

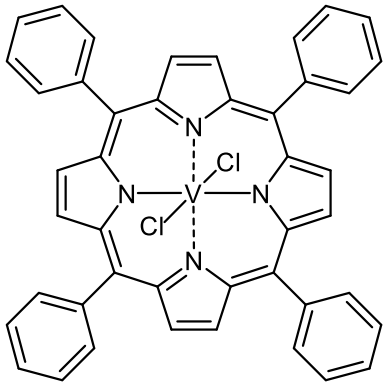


5,10,15,20-Tetra(4-diethylaminophenyl)-21*H*,23*H*-porphine vanadium(IV) oxide

Following the general procedure for synthesis of vanadium dichloride complexes with 5,10,15,20-tetra(4-diethylaminophenyl)-21*H*,23*H*-porphine, the complex was obtained as dark purple crystals. Yield: 199 mg (91%). FTIR, ν/cm^{-1}: 2960 m, 1599 m, 1525 m, 1245 s, 1191 m, 1001 s, 797 w.[225]

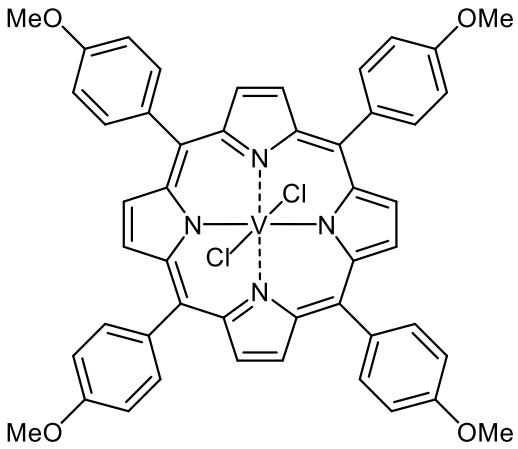
General procedure for synthesis of vanadium dichloride complex 48-51

Vanadium oxide complex (0.20 mmol) was dissolved in freshly degassed toluene (15 mL). $SOCl_2$ (0.15 mL, 2.0 mmol) was added. The resulting mixture was stirred for 24 h at room temperature under nitrogen atmosphere, and then placed in a refrigerator. The precipitate was filtered off, washed with hexane and dried.



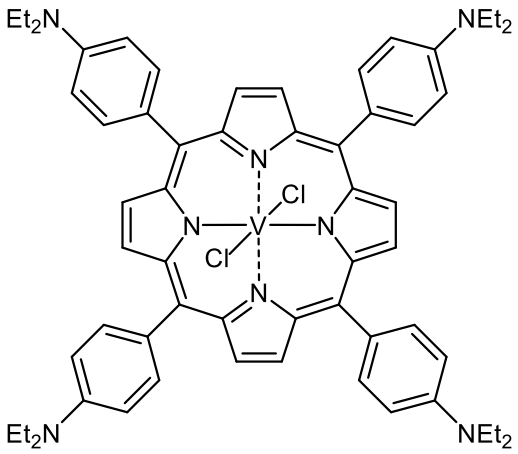
5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine vanadium(IV) dichloride (48)

Following the general procedure for synthesis of vanadium dichloride complexes with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine vanadium(IV) oxide, the catalyst was obtained as dark purple crystals. Yield: 75 mg (51%). FTIR, ν/cm^{-1}: 2846 w, 1593 m, 1438 m, 1335 m, 1173 m, 805 s, 747 s, 700 m.[219]



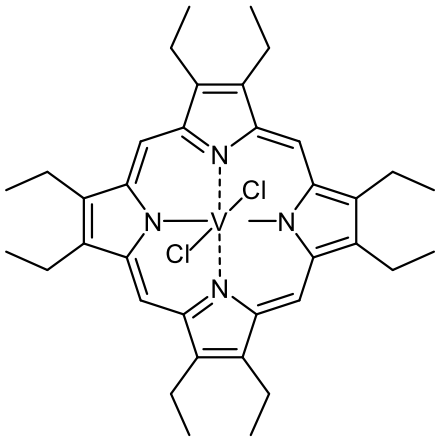
5,10,15,20-Tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphine vanadium(IV) dichloride (49)

Following the general procedure for synthesis of vanadium dichloride complexes with 5,10,15,20-tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphine vanadium(IV) oxide, the catalyst was obtained as dark purple crystals. Yield: 59 mg (34%). FTIR, ν/cm^{-1}: 2858 m, 1227 s, 1155 m, 768 w.



5,10,15,20-Tetra(4-diethylaminophenyl)-21*H*,23*H*-porphine vanadium(IV) dichloride (50)

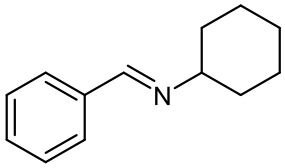
Following the general procedure for synthesis of vanadium dichloride complexes with 5,10,15,20-tetra(4-diethylaminophenyl)-21*H*,23*H*-porphine vanadium(IV) oxide, the catalyst was obtained as dark purple crystals. Yield: 86 mg (42%). FTIR, ν/cm^{-1}: 2967 m, 1608 m, 1521 m, 1263 s, 1194 m, 799 w.



2,3,7,8,12,13,17,18-Octaethyl-21*H*,23*H*-porphine vanadium(IV) dichloride (51)

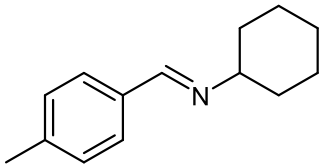
Following the general procedure for synthesis of vanadium dichloride complexes with 2,3,7,8,12,13,17,18-octaethyl-21*H*,23*H*-porphine vanadium(IV) oxide, the catalyst was obtained as dark maroon crystals. Yield: 104 mg (79%). FTIR, ν/cm^{-1}: 2962 m, 2867 m, 1464 m, 1313 m, 1140 s, 844 m, 726 m, 693 w.[219]

5.4.9 Characterization data



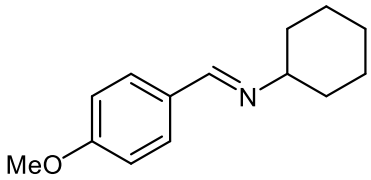
***N*-Benzylidenecyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 174 mg (93%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.32 (s, 1H), 7.74-7.72 (m, 2H), 7.40-7.39 (m, 3H), 3.24-3.16 (m, 1H), 1.84-1.55 (m, 7H), 1.43-1.24 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.7, 136.7, 130.4, 128.6, 128.2, 70.1, 34.5, 25.8, 25.0. MS: *m/z* = 187 $[M]^+$. NMR data are in accordance with literature values.[118]



***N*-(4-Methylbenzylidene)-cyclohexylamine**

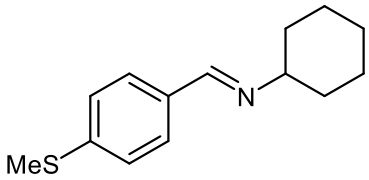
Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 130 mg (65%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.28 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 3.21-3.13 (m, 1H), 2.37 (s, 3H), 1.86-1.54 (m, 7H), 1.42-1.23 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.7, 140.6, 134.1, 129.3, 128.1, 70.1, 34.5, 25.8, 25.0, 21.6. MS: *m/z* = 201 $[M]^+$. NMR data are in accordance with literature values.[118]



***N*-(4-Methoxybenzylidene)-cyclohexylamine**

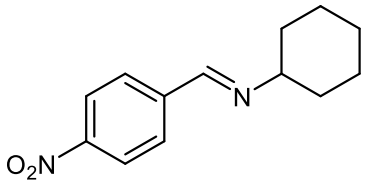
Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 178 mg (82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.24 (s, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 3.18-3.11 (m, 1H), 1.86-1.53 (m, 7H), 1.41-1.22 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 161.5, 158.0, 132.1, 129.7, 114.0, 70.0, 55.5, 34.6, 25.8, 25.0. MS: *m/z* = 217 $[M]^+$. NMR data are in accordance with literature values.[118]



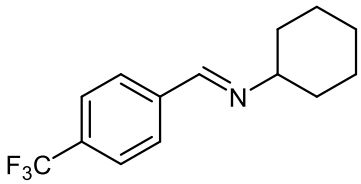
***N*-(4-Methylthiobenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a pale yellow solid. Yield: 182 mg (78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.25 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.25 (m, 2H), 3.21-3.13 (m, 1H), 2.50 (s, 3H), 1.85-1.53 (m, 7H), 1.41-1.23 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.2, 129.0, 128.6, 126.0, 123.8, 70.0, 34.5, 25.8, 25.0, 15.5. MS: *m/z* = 234 $[M]^+$. NMR data are in accordance with literature values.[118]



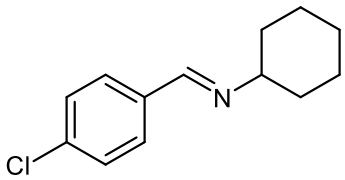
***N*-(4-Nitrobenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a pale yellow solid. Yield: 168 mg (72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.38 (s, 1H), 8.25 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 2H), 3.31-3.24 (m, 1H), 1.87-1.55 (m, 7H), 1.43-1.25 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 156.4, 149.0, 142.3, 128.8, 123.9, 70.3, 34.3, 25.7, 24.7. MS: *m/z* = 232 $[M]^+$. NMR data are in accordance with literature values.[118]



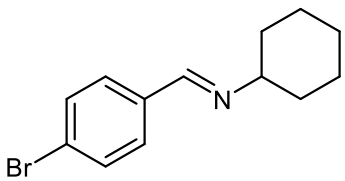
***N*-(4-Trifluoromethylbenzylidene)cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 195 mg (77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.35 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 3.28-3.20 (m, 1H), 1.87-1.55 (m, 7H), 1.42-1.22 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 157.2, 139.9, 132.1 (q, *J* = 33 Hz), 128.4, 125.6 (q, *J* = 4 Hz), 124.2 (q, *J* = 270 Hz), 70.2, 34.4, 25.7, 24.8. MS: *m/z* = 248 $[M-H]^+$. NMR data are in accordance with literature values.[186]



***N*-(4-Chlorobenzylidene)-cyclohexylamine**

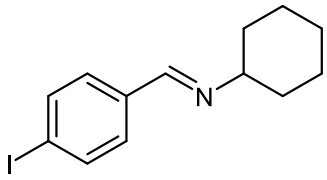
Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 155 mg (70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 3.23-3.15 (m, 1H), 1.86-1.52 (m, 7H), 1.42-1.24 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 157.3, 136.3, 135.2, 129.4, 128.9, 70.1, 34.5, 25.8, 24.9. MS: *m/z* = 222 $[M]^+$. NMR data are in accordance with literature values.[118]



***N*-(4-Bromobenzylidene)-cyclohexylamine**

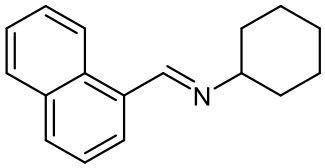
Following the general procedure for imine synthesis, the product was isolated as a pale yellow solid. Yield: 218 mg (82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.25 (s, 1H), 7.61-7.51 (m, 4H),

3.23-3.15 (m, 1H), 1.86-1.52 (m, 7H), 1.41-1.24 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 157.5, 135.6, 131.9, 129.6, 124.8, 70.1, 34.4, 25.7, 24.9. MS: *m/z* = 265 $[M]^+$. NMR data are in accordance with literature values.[118]



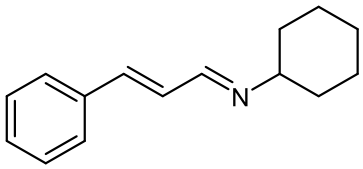
***N*-(4-Iodobenzylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the imine was isolated as a white solid. Yield: 226 mg (72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.23 (s, 1H), 7.73 (d, *J* = 8.4, 2H), 7.45 (d, *J* = 8.4, 2H), 3.22-3.15 (m, 1H), 1.85-1.52 (m, 7H), 1.41-1.27 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 157.7, 137.8, 136.2, 130.9, 129.8, 70.1, 34.4, 25.7, 24.9. GC-MS (EI, Pos): RT = 14.9 min, *m/z* = 313 $[M]^+$. NMR data are in accordance with literature values.[102]



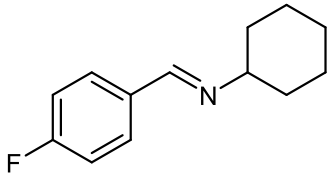
***N*-(1-Naphthalenylmethylene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 200 mg (84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 9.00 (s, 1H), 8.88 (d, *J* = 8.5 Hz, 1H), 7.91-7.88 (m, 3H), 7.61-7.49 (m, 3H), 3.35-3.28 (m, 1H), 1.92-1.67 (m, 7H), 1.49-1.32 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 158.0, 133.9, 132.3, 131.5, 130.7, 128.7, 128.4, 127.0, 126.0, 125.4, 124.4, 71.0, 34.7, 25.8, 24.9. MS: *m/z* = 237 $[M]^+$. NMR data are in accordance with literature values.[118]



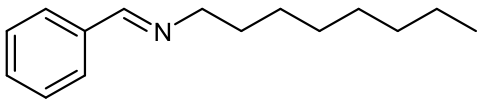
***N*-(Cinnamylidene)-cyclohexylamine**

Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 189 mg (89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.05 (t, *J* = 4.2 Hz, 1H), 7.47-7.44 (m, 2H), 7.37-7.26 (m, 3H), 6.92 (d, *J* = 4.2 Hz, 2H), 3.10-3.02 (m, 1H), 1.83-1.24 (m, 10H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 160.5, 141.2, 136.0, 129.1, 128.9, 128.7, 127.3, 69.8, 34.6, 25.7, 24.9. MS: *m/z* = 216 $[M-H]^+$. NMR data are in accordance with literature values.[103]



***N*-(4-Fluorobenzylidene)-cyclohexylamine**

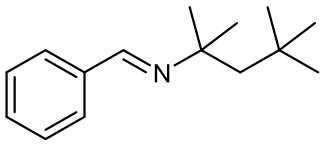
Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 45 mg (22%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 (s, 1H), 7.71 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 3.21-3.15 (m, 1H), 1.86-1.55 (m, 7H), 1.41-1.24 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 165.5 (d, *J* = 253 Hz), 157.3, 133.0 (d, *J* = 3 Hz), 130.0 (d, *J* = 9 Hz), 115.8 (d, *J* = 21 Hz) 70.0, 34.5, 25.8, 25.0. MS: *m/z* = 205 $[M]^+$. NMR data are in accordance with literature values.[118]



***N*-Benzylidene-octylamine**

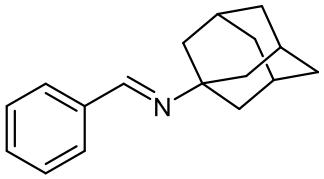
Following the general procedure for imine synthesis, the product was isolated as a yellow liquid. Yield: 159 mg (74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 (s, 1H), 7.74-7.72 (m, 2H), 7.42-7.39 (m, 3H), 3.61 (t, *J* = 6.9 Hz, 2H), 1.74-1.67 (m, 2H), 1.38-1.28 (m, 10H), 0.90-0.86 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 160.8, 136.5, 130.6, 128.7, 128.1, 62.0, 32.0, 31.1, 29.6, 29.4, 27.5, 22.8, 14.2. MS: *m/z* = 216 $[M-H]^+$. NMR data are in accordance with literature values.[118]



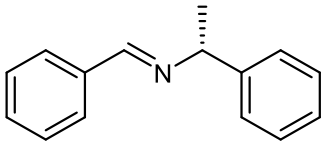
_N_-Benzylidene-_tert_-octylamine

Following the general procedure for imine synthesis, the product was isolated as a clear liquid. Yield: 125 mg (62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.26 (s, 1H), 7.77-7.74 (m, 2H), 7.42-7.40 (m, 3H), 1.71 (s, 2H), 1.34 (s, 6H), 0.97 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 154.5, 137.6, 130.1, 128.6, 128.0, 61.1, 56.8, 32.2, 32.0, 29.8. MS: *m/z* = 216 $[M-H]^+$. NMR data are in accordance with literature values.[118]



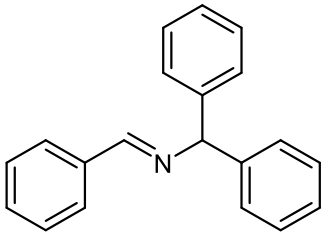
_N_-Benzylidene-1-adamantanylamine

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 146 mg (61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.29 (s, 1H), 7.76-7.74 (m, 2H), 7.40-7.39 (m, 3H), 2.18 (s, 3H), 1.83-1.82 (m, 6H), 1.78-1.69 (m, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 155.0, 137.4, 130.2, 128.6, 128.0, 57.6, 43.3, 36.7, 29.7. MS: *m/z* = 239 $[M]^+$. NMR data are in accordance with literature values.[118]



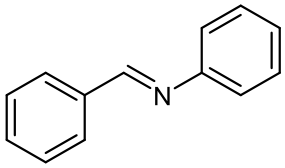
(*R*)-*N*-Benzylidene-1-phenylethylamine

Following the general procedure for imine synthesis, the product was isolated as a clear liquid. Yield: 125 mg (60%). $[\alpha]_D^{20}$ = -67.2 (*c* = 1.59, $CHCl_3$) (ref.[190] $[\alpha]_D^{27}$ = -64.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.24 (s, 1H), 7.67-7.65 (m, 2H), 7.32-7.20 (m, 7H), 7.13-7.09 (m, 1H), 4.42 (q, *J* = 6.6 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 159.6, 145.3, 136.5, 130.7, 128.6, 128.5, 128.4, 126.9, 126.8, 69.9, 25.0. MS: *m/z* = 209 $[M]^+$. NMR data are in accordance with literature values.[118]



***N*-Benzylidene-1,1-diphenylmethylamine**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 250 mg (92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.34 (s, 1H), 7.77-7.74 (m, 2H), 7.33-7.31 (m, 7H), 7.23 (t, *J* = 7.6 Hz, 4H), 7.16-7.12 (m, 2H), 5.52 (s, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 160.9, 144.0, 136.4, 130.9, 128.7, 128.6, 128.6, 127.8, 127.1, 78.0. MS: *m/z* = 271 $[M]^+$. NMR data are in accordance with literature values.[118]



***N*-Benzylideneaniline**

Following the general procedure for imine synthesis, the product was isolated as a white solid. Yield: 102 mg (57%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.38 (s, 1H), 7.85-7.82 (m, 2H), 7.41-7.39 (m, 3H), 7.34-7.30 (m, 2H), 7.16-7.13 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 160.6, 152.2, 136.3, 131.5, 129.3, 129.0, 128.9, 126.1, 121.0. MS: *m/z* = 187 $[M]^+$. NMR data are in accordance with literature values.[118]

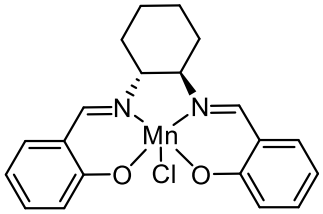
6. Conclusion

The purpose of this project was to develop novel and inexpensive catalysts based on Earth-abundant transition metals for acceptorless dehydrogenative tranformations of alcohols.

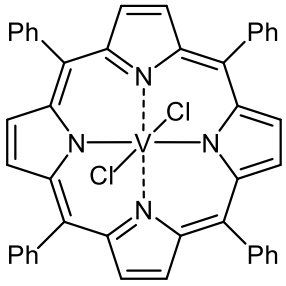
As a result, two novel catalysts based on manganese (**19**) and vanadium (**48**), respectively, have been developed for the dehydrogenative synthesis of imines.

Catalyst **19** is the first example of a manganese(III) complex for acceptorless alcohol dehydrogenation. It is a cheap and very stable complex in strong contrast to the currently used manganese(I) catalysts, which are based on expensive phosphine ligands. The reaction mechanism has been investigated thoroughly, and a MLC pathway has been proposed.

Catalyst **48** constitutes the first example of a vanadium catalyst for acceptorless dehydrogenation of alcohols. Consequently, vanadium can be added to the list of base metals able to do acceptorless alcohol dehydrogenation. The reaction mechanism has been investigated suggesting an alkoxide intermediate in the catalytic cycle.



19



48

In summary, this study has contributed with two novel and more sustainable catalysts as an alternative to the traditional oxidants in organic synthesis.

Publications

Samuelsen, S. V.; Santilli, C.; Ahlquist, M. S. G.; Madsen, R. Development and mechanistic investigation of the managense(III) salen-catalyzed dehydrogenation of alcohols. *Chem Sci*., **2019**, *10*, 1150-1157.

Appendix A1: External stay at Haldor Topsøe A/S

The following work was performed at Haldor Topsøe A/S as an external stay under the supervision of R&D manager Søren Tolborg and R&D director Esben Taarning.

As mentioned in section **3.3**, in view of the microscopic reversibility principle, potentially, dehydrogenations and hydrogenations can be carried out with the same catalysts. Therefore, we decided to investigate whether the already described complexes **19**, **36, 42** and **48** as well as complex **54-58**, which either already has been investigated or is currently being investigated in the Madsen group for potential use as a dehydrogenation catalysts (Figure **6.1**) could mediate the reduction of different functional groups under a hydrogen atmosphere.

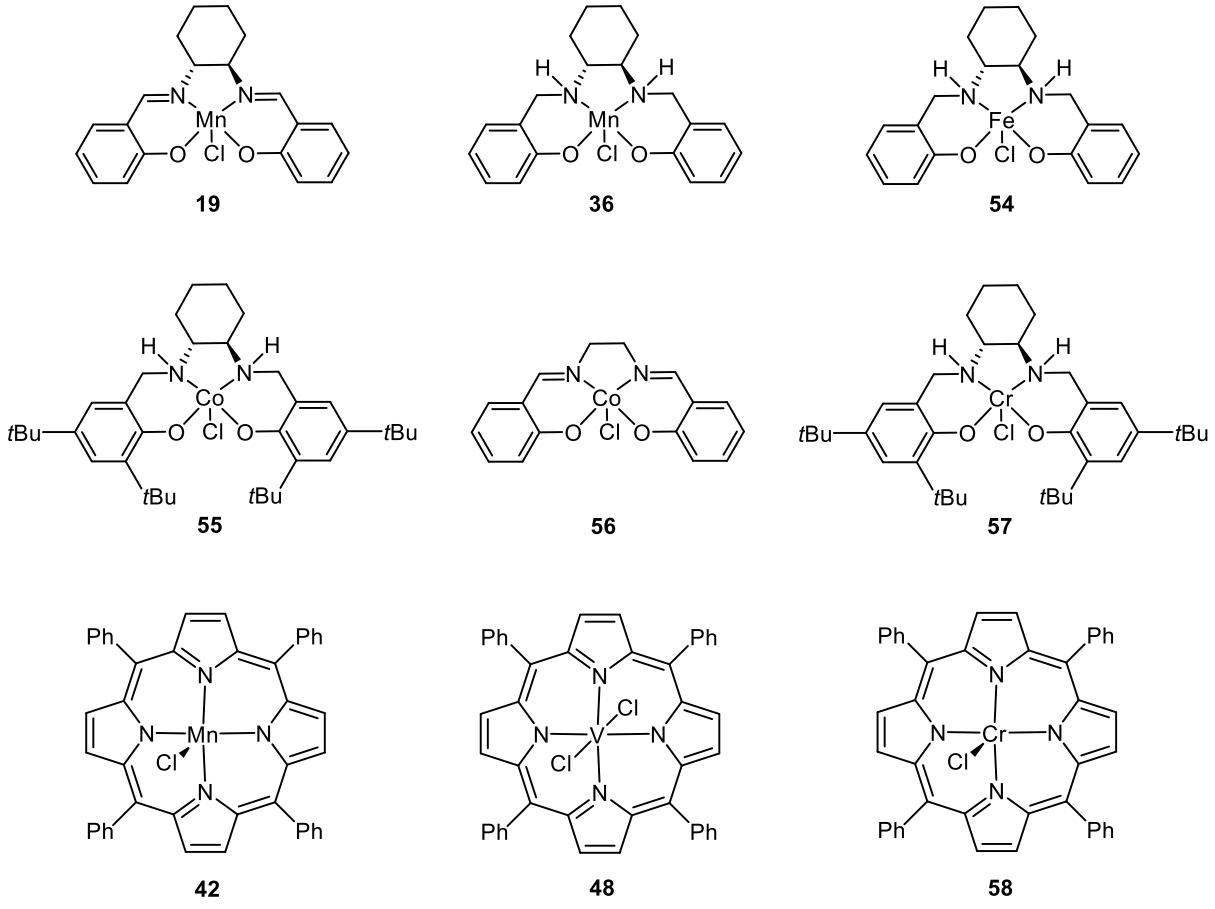
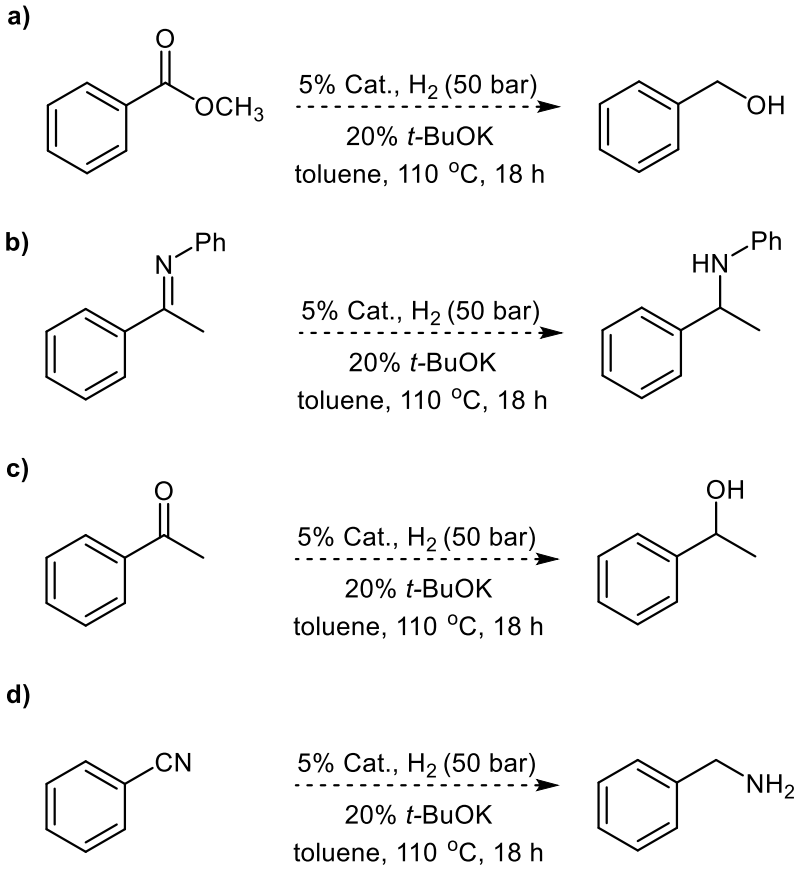


Figure 6.1. Complexes investigated in hydrogenation reactions.

In our investigation, an ester, an imine, a ketone and a nitrile were selected as substrates in our hydrogenation reactions. The reactions were carried out with 5% catalyst and 20% *t*-BuOK under 50 bars of H_2 in refluxing toluene (Scheme **6.1**).



Scheme 6.1. Attempted hydrogenations of a) an ester, b) an imine, c) a ketone and d) a nitrile.

Unfortunately, regardless the harsh conditions, none of the complexes showed any activity in any of the four investigated transformations.

Experimental section

General experimental methods

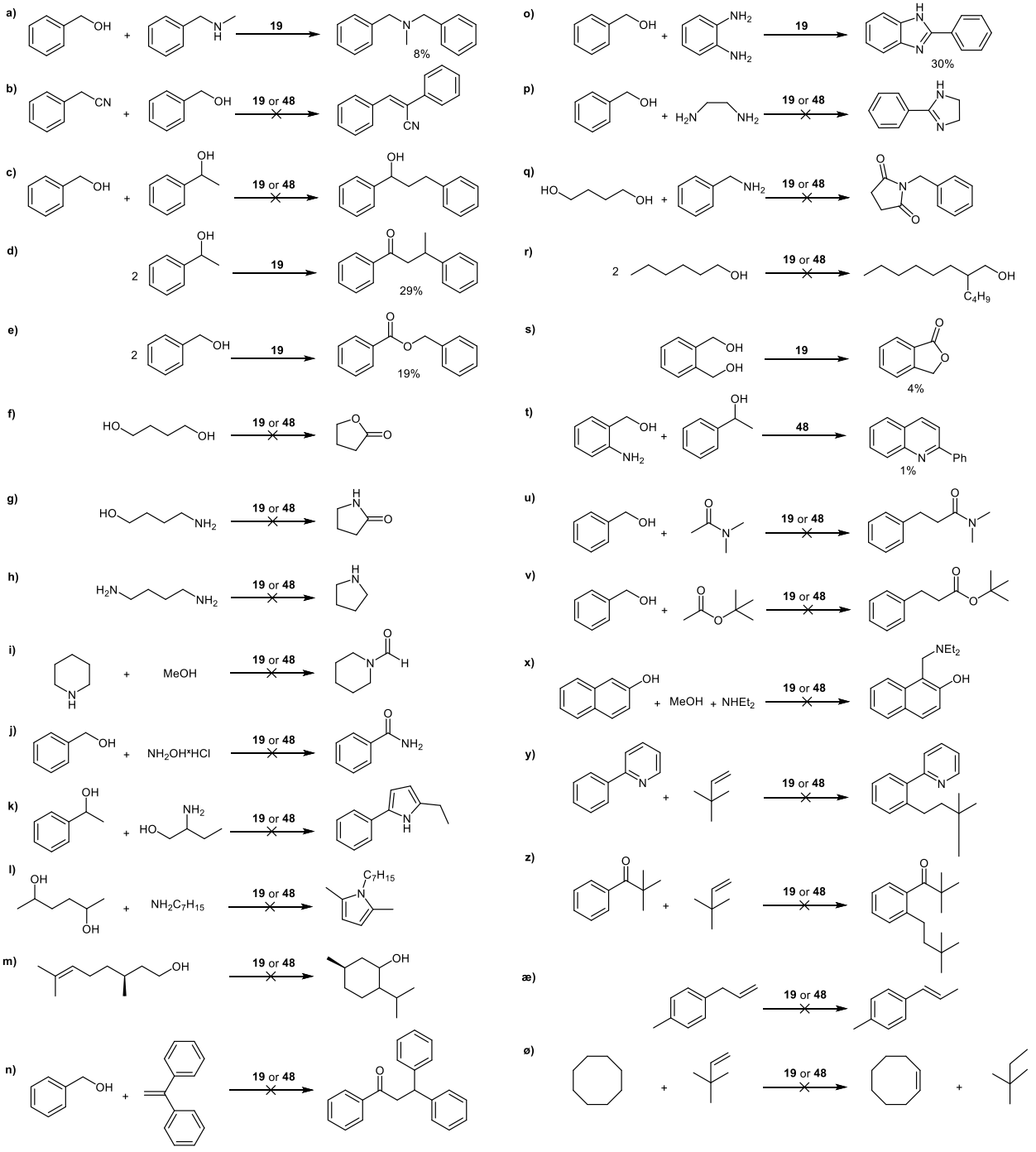
All commercial reagents were purchased from Sigma-Aldrich or Strem Chemicals and used as received. GC-MS was carried out on a Shimadzu GCMS-QP2010S instrument fitted with an Equity 5, 30m×0.25mm×0.25μm column. All experiments were carried out under hydrogen pressure in a Parr reactor.

General procedure

Methyl benzoate (0.88 mL, 7 mmol), imine (1365 mg, 7 mmol), acetophenone (0.84 mL, 7 mmol) or benzonitrile (0.72 mL, 7 mmol), catalyst **19**, **36**, **42**, **48**, **54**, **55**, **56**, **57** or **58** (0.35 mmol), *t*-BuOK (70 mg, 0.7 mmol), tetradecane (0.7 mL) as internal standard and toluene (16 mL) were placed in an oven-dried Parr reactor. Vacuum was applied and the flask was then filled with nitrogen gas (repeated three times) and subsequently with H_2 (repeated three times). The reactor was heated to 110 ºC and pressureized with H_2 (50 bar). The reaction was stirred for 18 h, after which the mixture was cooled to room temperature and the H_2 was carefully released. The reaction mixture was then examined by GC-MS.

Appendix A2

A selection of reactions in which complex **19** and **48** has been tested as catalyst is listed below. In all cases, various conditions have been tried.



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