Ruthenium-catalyzed hydrogen transfer involving amines and imines. Mechanistic studies and synthetic applications.

Joseph S. M. Samec

Department of Organic Chemistry
Arrhenius Laboratory
Stockholm University, April 2005
Abstract

This thesis deals with ruthenium-catalyzed hydrogen transfer involving amines and imines and is divided into two parts. In Part 1 a mechanistic study has been performed. The complexation of the imine to the catalyst and the decomplexation patterns of the formed ruthenium-amine complexes, isotope studies, and exchange studies show that the mechanism of the hydrogen transfer involving amines and imines is different from the hydrogen transfer involving alcohols and carbonyls.

In Part 2 synthetic applications of the hydrogen transfer is presented. First the ruthenium-catalyzed transfer hydrogenation of imines by 2-propanol in an unpolar solvent was investigated. The corresponding amines were isolated in good to excellent yields. Even imines bearing labile functional groups were smoothly transferred to amines with very low catalyst loadings and short reaction times employing microwave heating. Then the reverse reaction, transfer dehydrogenation of amines to imines, was investigated using either MnO₂ or oxygen as terminal oxidant. Important products such as aldmines, ketimines, and non benzylic anilines were prepared in the aerobic oxidation. We also demonstrated that the aerobic oxidation is compatible with proline-mediated organocatalysis, yielding amines in high yields and ee:s. Finally the racemization of chiral amines was investigated. A cumbersome side product formation was investigated and hampered by the use of a mild hydrogen donor, giving a mild and efficient racemization process for both primary and secondary amines.
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List of publications
This thesis is based on the following papers, referred to in the text by their Roman numerals I-VII.


VI Enantioselctive addition of aldehydes to amines via combined catalytic biomimetic oxidation and organocatalytic C-C- bond formation. Ismail Ibrahim, Joseph S. M. Samec, Jan-E. Bäckvall, Armando Córdova, submitted for publication.


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Preface

This thesis describes the work reported in publications I-VII listed on the preceding page. My ambition is to summarize all the results that will help the reader to get interested in this field and to understand these transformations. I also want to emphasize the work I have been responsible for.

In paper I, Dr. H. Éll and I collaborated equally. In paper II I worked independently. In paper III Ms. Mony worked under my supervision as a diploma worker. In paper IV I am responsible for preparing the starting material and catalyst and Dr. H. Éll performed the catalysis. In paper V and paper VI I am responsible for all starting material synthesis and the aerobic oxidation of amines. Dr. H. Éll performed the substrate tolerance screening in paper V and Mr. Ibrahem is responsible for the organocatalysis in paper VI. In paper VII I did parts of the starting material, performed some of the racemization experiments, and all the work on the combination of racemization with enzymatic kinetic resolution.
Appendix A

List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>BQ</td>
<td>1,4-benzoquinone</td>
</tr>
<tr>
<td>CALB</td>
<td><em>Candida Antartica</em> Lipase B</td>
</tr>
<tr>
<td>ETM</td>
<td>electron-transfer-mediator</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>M</td>
<td>metal</td>
</tr>
<tr>
<td>MVP</td>
<td>Meerwein-Verley-Ponndorf</td>
</tr>
<tr>
<td>NAD</td>
<td>α-nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-pyrrolidinone</td>
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</tr>
<tr>
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<td>tert-butyldimethylsilyl</td>
</tr>
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</table>
Appendix B

[2,3,4,5-Ph₄(η⁴-C₄CO)]Ru(CO)₂NH(Ph)(CHCH₃Ph) (11). Imine 7 (0.1 mL, 0.03 mmol, 0.3 M in CD₂Cl₂) was added to a solution of 6 (0.5 mL, 0.06 mmol, 0.12 M in CD₂Cl₂) at -199 °C under Ar. The NMR tube was inserted to a pre-cooled spectrometer (-50 °C) and the temperature was let up to -39 °C where the complex appeared. ¹H NMR (CD₂Cl₂, 400 MHz, O °C) major isomer δ 0.86 (d, J = 6.5 Hz, CH₃), 3.46 (d, J = 11.0 Hz, NH), 4.55 (m, CH), 5.62 (m, Ar), 5.98 (m, Ar) 6.42-8.00 (m, Ar) the other aromatic resonances were obscured by 6 and the other isomer. Minor isomer: δ 1.49 (d, J = 6.5 Hz, CH₃), 4.48 (m, CH) 6.42-8.00 (m, Ar) the other aromatic resonances were obscured by 6 and the other isomer. The spectrometer was then heated to –30 °C where the free amine 12 δ 1.53 (d, J = 7.3 Hz, CH₃) and 5 δ -18.75 (s, RuH) appeared.

Hydrogenation of 17 by 6 in the presence of 16. Complex 6 was prepared in CD₂Cl₂ (0.4 mL). The 0.2 M solution of 6 was added by syringe into an NMR-tube under Ar and cooled to –199 °C. Freshly distilled 17 (0.1 mmol, 1 M, 0.1 mL) and 16 (0.1 mmol, 1 M, 0.1 mL) were added and the sample was warmed to –78 °C and carefully shaken. The sample was put into a spectrometer pre-cooled to –20 °C and the reaction was analyzed by ¹H NMR integrating the doublets at δ 0.88 for 19 and at δ 0.93 for 18.

[2,3,4,5-Ph₄(η⁴-C₄CO)]Ru(CO)₂NH(CH₃)(CHPhCH₃) (18). ¹H NMR (400 Hz, CDCl₃, 25 °C) major isomer: δ 1.56 (d, J = 7.3 Hz, CH₃), 2.07 (d, J = 5.5 Hz, NCH₃), 3.88 (m, J = 5.5 and 7.3 Hz, CH), 6.84-6.87 (m, 4H, Ar), 7.0-7.29 (m, 16H, Ar), 7.54-7.57 (m, 2 H, Ar), 7.59-7.64 (m, 1H Ar), 7.0-7.5 (m, 2 H, Ar), minor isomer: δ 0.90 (d, J = 6.8 Hz, CH₃) 2.15 (d, J = 5.9 Hz, NCH₃), 3.65-3.75 (m, CH), 7.04-7.24 (m, 23 H, Ar), 7.61-7.63 (m, 2 H, Ar).

[2,3,4,5-Ph₄(η⁴-C₄CO)]Ru(CO)₂NH(CH₃)(CH(4-MeO-Ph)(CH₃)) (19). ¹H NMR (400 Hz, CDCl₃, 25 °C) major isomer: δ 1.53 (d, J = 7.1 Hz, CH₃), 2.06 (s, NCH₃), 3.74 (s, OCH₃), 3.85 (q, J = 7.1, CH), 6.70-6.78 (m, 4H, Ar), 7.0-7.24 (m, 16H, Ar), 7.55-7.57 (m, 2H, Ar), 7.73-7.78 (m, 2H, Ar), minor isomer: δ 0.95 (d, J = 6.7 Hz,CH₃) 2.17 (d, J = 5.8, NCH₃), 3.62-3.73 (m, CH), 3.73 (s, OCH₃), 6.67-6.78 (m, 2H, Ar), 6.97-7.29 (m, 18H, Ar), 7.51-7.65 (m, 2H, Ar), 7.70-7.75 (m, 2H, Ar).
Introduction

I.1 Reduction and oxidation

Even though hydrogen (H) is the smallest atom in the periodic table and exists as the tiniest known molecule (H₂), it has a profound impact in chemistry. For example, the hydrogen molecule formally is the difference between the saturated and unsaturated form of many different substrate classes. If the hydrogen atom loses an electron, a proton is generated and if the hydrogen atom gains an electron, a hydride is formed. Together the hydride and the proton form hydrogen gas (eq. 1).

\[
\text{H}^+ + \text{H}^- \rightarrow \text{H}_2
\]

(eq. 1)

The difference between an imine and an amine is formally hydrogen gas (Scheme 1). It is quite amazing that the smallest molecule has such a profound effect on the substrate since the reduced form, the amine, acts as a nucleophile and the oxidized form, the imine, acts an electrophile with opposite reactivity in organic transformations. Because the presence or absence of hydrogen is crucial for the type of reactivity of these compounds, it is of great interest to be able to control the hydrogen transfer between imines and amines. The addition of H₂ to an imine, generating an amine, is termed reduction and the opposite, when H₂ is abstracted from an amine, forming an imine, is termed oxidation.¹

Scheme 1. Hydrogen transfer involving imines and amines.

I.2 Catalysis

In 1836 Berzelius defined catalysis² as “Catalytic power actually means that substances are able to awaken affinities which are asleep at this temperature by their mere presence…” Today catalysis is usually defined as a process where the catalyst increases the rate of a reaction without being consumed itself. Catalysts range from simple acids and bases that promote proton transfers in many different reactions to transition metals with chiral ligands that catalyze processes where only one of two possible enantiomers of a product is formed. In this thesis a ruthenium catalyst is used for the hydrogen transfer involving amines and imines.

I.3 Reduction of imines

The logical approach to reduce an imine to the corresponding amine is by adding H₂.³ This is a standard procedure found in the literature and which is used in industry. A variety of different metal catalysts based on Pd, Ir, Rh, Ru, Ti, and Zn have been used.⁴ The E factor,⁵ defined by the mass of the waste divided by the mass of the product, is very low since the reactions generally go to completion and no waste is generated. As hydrogen is explosive, the handling
requires expensive and specialized equipment. Another drawback with this methodology is that the reactivity of hydrogen gas lowers the chemoselectivity if other functional groups are present.\textsuperscript{6} One of the most common procedures for the reduction of imines involves a metal hydride, where different borohydrides are by far the most popular.\textsuperscript{7} These reactions are unfortunately stoichiometric and produce a lot of waste, giving a high E factor.\textsuperscript{5} Moreover, the workup requires tedious acid/base extractions that lower the yields and further increase the E factor. An additional drawback with this procedure is that acid/base labile functional groups are not tolerated. An attractive way to circumvent the hazardous use of hydrogen and the stoichiometric use of metal hydrides is to employ hydrogen transfer reduction where 2-propanol can serve as hydrogen source with the aid of a metal catalyst (Scheme 2).\textsuperscript{6} 2-Propanol is cheap, nontoxic, and volatile. It has good solvent properties, does not affect the pH, and dehydrogenates to acetone. The latter is fairly unreactive, and easily removed by distillation during workup. Even though the acetone formed increases the E factor compared to hydrogenation reactions, the environmental unfriendliness quotient (EQ) of acetone is very low.\textsuperscript{8} Despite the advantages of this methodology and the importance of this transformation, there are only few reports regarding the development or the use of this methodology.\textsuperscript{9,10}

\textbf{Scheme 2.} Transfer hydrogenation of imines to amines.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{N}};
  \node (b) at (0.5,0) {\text{R}_3};
  \node (c) at (1,0) {\text{R}_2};
  \node (d) at (0.5,-0.5) {\text{OH}};
  \node (e) at (0,1) {\text{R}_1};
  \node (f) at (0.5,1) {\text{R}_3};
  \node (g) at (1,1) {\text{R}_2};
  \node (h) at (1.5,1) {\text{O}};
  \node (i) at (1.5,0) {\text{R}_1};
  \node (j) at (1.5,-0.5) {\text{HN}};
  \node (k) at (1.5,0.5) {\text{HN}};

  \draw (a) -- (b) -- (c);
  \draw (d) -- (e) -- (f) -- (g) -- (h);
  \draw (i) -- (j) -- (k);

  \node at (0.5,-1) {\text{catalyst}};
\end{tikzpicture}
\end{center}

\textbf{I.4 Oxidations of amines}

Oxidation of an amine by molecular oxygen with the aid of a transition metal catalyst would be ideal from both environmental and economical points of view. The only byproduct would be water. The challenge to overcome when using a substrate-selective transition metal catalyst is the usually high energy barrier for the reoxidation of the reduced form of the metal by molecular oxygen. For the aerobic oxidation of amines there are two examples in the literature where the reduced metal is directly oxidized by molecular oxygen. Unfortunately, both methodologies are unsatisfactory since hydrolysis and overoxidation of the formed imine occurred.\textsuperscript{11,12} An efficient and successful way to circumvent the high energy pathway for reoxidation of the metal is to mimic biological oxidations, where large jumps in oxidation potentials are avoided by dividing the high energy barrier to several coupled redox catalysts as electron transfer mediators (ETMs) (Scheme 3). This is the method adopted in living organisms in the alcohol oxidation by the alcohol dehydrogenase enzyme with NAD\textsuperscript{+} as cofactor to give the corresponding ketone and NADH + H\textsuperscript{+}. The cofactor is then subsequently reoxidised by ubiquinone. The reduced ubiquinone (ubiquinol) transfers the electrons to cytochrome c, which is oxidized by molecular oxygen.

\textbf{I.5 Amines and imines}

Amines are the organic derivatives of ammonia. They have a trigonal pyramidal shape with an unshared electron pair occupying an sp\textsuperscript{3} orbital that is considerably extended into space. This unshared electron pair is an important feature of amines and this is probably why they are so often used in pharmaceuticals, where the free electron pair can coordinate to electrophilic centers in various active sites within the body.
A common pathway to amines is via imines, which play an important role as intermediates, acting as electrophilic reagents in many different reactions including reductions, additions, condensations, and cycloadditions (see Scheme 4 for some examples). Many of these transformations can be carried out with high enantioselectivity. Imines also occur as intermediates in the racemization of chiral amines. The standard protocol for preparing imines is by condensation between an amine and an aldehyde or a ketone. However, the very electrophilic nature of the product can cause problems during workup and purification. The electrophilic carbonyl counterpart (ketone or aldehyde) is reactive, so tedious protection is needed in a multistep synthesis. Therefore it would be of interest to generate imines from a more stable precursor.

Scheme 4. Different reactions of imines.

1) Hydrogenation\textsuperscript{10} 2) Mannich rxn\textsuperscript{14} 3) Strecker rxn\textsuperscript{15} 4) Imino Ene rxn\textsuperscript{16} 5) Addition 6) [2 + 2] addition\textsuperscript{17} 7) aza-Baylis-Hillman rxn\textsuperscript{18} 8) aza-Diels-Alder.\textsuperscript{19}
Part 1

Chapter 1 Mechanistic aspects\textsuperscript{I,II}

1.1 Introduction

1.1.1 Hydrogen transfer. While the mechanistic study on hydrogen transfer involving amines and imines is very limited, extensive studies have been performed on the corresponding reaction concerning alcohols and ketones (aldehydes).\textsuperscript{6} This is probably because the latter reaction is more established and also due to the assumption that the mechanism of hydrogen transfer involving imines and amines resembles that of ketones (aldehydes) and alcohols. Therefore, this introduction will cover the mechanistic studies performed on the hydrogen transfer reaction involving ketones (aldehydes) and alcohols, dating back to the 1920s when it was found that aluminum alkoxides work as substrate-selective catalysts for the redox reaction of alcohols and ketones. Meerwein, Verley, and Ponndorf found that carbonyl compounds were reduced in the presence of 2-propanol (Scheme 5).\textsuperscript{20} Oppenauer later found that secondary alcohols were oxidized in the presence of acetone (Scheme 5).\textsuperscript{21}

Scheme 5

Later it has been shown that transition metals such as ruthenium, iridium, titanium, samarium, or rhodium are good candidates for substrate selective catalysts in these transformations,\textsuperscript{6} and the application of chiral ligands to the metal generating chiral catalysts that can be used in asymmetric catalysis has made the hydrogen transfer reaction a very popular transformation in organic chemistry.\textsuperscript{22}

1.1.2 Mechanism. Two main pathways have been proposed for hydrogen transfer to ketones (aldehydes) depending on the type of metal used. Direct hydrogen transfer is claimed to occur with main group elements and was proposed for the Meerwein-Verley-Ponndorf reduction.\textsuperscript{23} This is a concerted process involving a six-membered transition state, in which both the hydrogen donor and the hydrogen acceptor are coordinated to the metal center (Figure 1, left). The hydridic route includes transition metal catalysts and gives rise to a characteristic metal hydride that is involved in the hydrogen transfer (Figure 1, right).\textsuperscript{24}

Figure 1

Later it has been shown that transition metals such as ruthenium, iridium, titanium, samarium, or rhodium are good candidates for substrate selective catalysts in these transformations,\textsuperscript{6} and the application of chiral ligands to the metal generating chiral catalysts that can be used in asymmetric catalysis has made the hydrogen transfer reaction a very popular transformation in organic chemistry.\textsuperscript{22}
Our group found that the hydridic route can be further divided into metal monohydride and metal dihydride pathways depending on which catalyst that is used.\textsuperscript{25,26} In the monohydride mechanism, the metal hydride arises purely from the $\alpha$-C-H of the hydrogen donor (e.g. 2-propanol), and this M-H is only transferred to the carbonyl carbon of the substrate and thereby the hydride keeps its identity (Scheme 6, path A). In the dihydride pathway the metal hydride arise from both $\alpha$-C-H and the OH of the hydrogen donor, and therefore the catalyst does not distinguish between the proton and the hydride (Scheme 6, path B).

**Scheme 6**

There are two types of catalysts operating through the monohydride mechanism that have been suggested to operate differently. The formation of the metal monohydride from the hydrogen donor may involve the formation of a transition metal alkoxide followed by $\beta$-elimination to give the M-H. Alternatively, it may proceed through a concerted pathway with simultaneous transfer of proton and hydride from 2-propanol to a basic site of the ligand and to the metal, respectively, without coordination of the alcohol to the metal. In both pathways the metal hydride gives rise to the $\alpha$-C-H.

In the pathway via a transition metal alkoxide a coordinated carbonyl inserts into the metal hydride 1 and forms metal alkoxide 2 (Scheme 7). This insertion should proceed via

**Scheme 7.** Catalytic cycle via a metal alkoxide.
π-bonded ketone (metal bound to the double bond). 2-Propanol exchanges the alkoxide and releases the product. The metal isopropoxide then undergoes β-elimination forming the metal hydride 1. There is ample support for this alkoxide mechanism and it has been demonstrated that transition metal hydrides are obtained from β-elimination of the corresponding alkoxide complexes. Even ligand assisted versions of this transformation have been reported. Many transition metal catalysts are operating via a metal alkoxide in transfer hydrogenation, for example the Wilkinson catalyst Rh(PPh₃)₃Cl.

A common feature of catalysts that are proposed to operate through a concerted mechanism is that one of the donor atoms of the ligand acts as a basic center and activates the substrate. This mechanism was first proposed by Noyori for 16-electron Ru complexes such as 3 (Scheme 8). The reaction cycle involves a simultaneous transfer of the proton and the hydride from 4 to the carbonyl in a cyclic six-membered transition state forming the alcohol and 3. Then the proton and the hydride from 2-propanol are delivered to the ligand and the metal, respectively, in the same fashion forming 4 and acetone. Note that the reaction is proposed to proceed without coordination of either alcohol or ketone (aldehyde) to the metal (Scheme 8).

**Scheme 8.** Catalytic cycle via a concerted six-membered transition state.

Casey and co-workers provided experimental support for this pathway for Shvo’s catalyst 5 in the stoichiometric reaction of the metal hydride 6 with benzaldehyde. From kinetic studies it was found that there is a combined kinetic isotope effect for the two hydrogens transferred in the process, which supports a concerted mechanism. Our group demonstrated that there is a simultaneous transfer of the two hydrogens also for the reverse reaction where a secondary alcohol was oxidized to the corresponding ketone. Although supported by theoretical studies, these concerted mechanisms are still under discussion.
Scheme 9. Shvo’s dimeric catalyst precursor in equilibrium with the active species 6 and A.

### 1.2 Results and discussion

#### 1.2.1 Electronic effects of the substrate. During the transfer hydrogenation study of imines to amines by catalyst 5 a correlation between the electronic property of the substrate and the rate of the reaction was observed. For example, when the benzyl group of N-phenyl-(1-phenylethylidene)amine (7) was substituted in the para position with a methoxy group the rate measured in turnover frequency (TOF) increased from 700 h⁻¹ to 840 h⁻¹ (Table 1, entries 1 and 2) and when the p-methoxy group was exchanged for a p-fluoro group the TOF dramatically decreased to 120 h⁻¹ (Table 1, entry 4). Another observation was that ketimines reacted much faster than aldimines in the hydrogen transfer reactions (Table 1, entry 3). This is in sharp contrast to the carbonyl analogs, where for example aldehydes were 30 times faster than ketones in the stoichiometric reduction of 6 as reported by Casey and coworkers.⁹a

<table>
<thead>
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<th>entry</th>
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<th>Y</th>
<th>TOF b</th>
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<tbody>
<tr>
<td>1</td>
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<td>Me</td>
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</tr>
<tr>
<td>2</td>
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<td>Me</td>
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</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Me</td>
<td>120 c</td>
</tr>
</tbody>
</table>

Table 1 Electronic effect on the rate.a

a The reactions were run using imine (0.3 mmol), 5 (0.9 µmol), and 2-propanol (7.2 mmol, 0.55 mL, 24 equiv.), in benzene (0.95 mL), at 70 °C. b TOF was measured after 10 min by ¹H NMR and based on catalyst 5. c 1 mol% of 5 was used.

Interestingly, this trend was also found in the transfer dehydrogenation of amines to imines where the TOF was increased from 33 h⁻¹ to 51 h⁻¹ by substituting the benzyl group in the para position by a methoxy group.V A p-methoxy group at the aniline-ring instead of H further increased the TOF to 71 h⁻¹.

In accordance, the same trend was found in the racemization of chiral amines where the racemization after one hour was 44% for the p-methoxy substituted phenylethyl amine compared to 18% for unsubstituted phenylethyl amine.VII

The influence of the electronic property of the substrate on the rate for the different reactions intrigued us. The concerted mechanism did not adequately explain the electronic effect in the hydrogen transfer reactions involving imines and amines. We argued that a more polarized
bond would react faster in a ligand-metal bifunctional outer-sphere mechanism. This is in contrast to the reactivity order observed *i.e.* imines > aldehydes > ketones and ketimines > aldimines. Therefore, we considered other possible mechanisms for this transformation and the corresponding pathway through a ruthenium-amine complex (*cf.* transition metal alkoxide in Scheme 7) seemed appealing. It is expected that an electron-rich imine would coordinate better to ruthenium explaining the observed electronic effect where electron-rich substrates react faster. This mechanism would also explain the difference in reactivity for aldimines and ketimines where ketimines are better nucleophiles and therefore would coordinate stronger to ruthenium than aldimines.

### 1.2.2 Isomerization.

In the transfer hydrogenation of imine 8 with 5 as catalyst, we observed an isomerization of 8 to 9. The imine 9 appears to be more stable than 8. When starting from 8 there is a fast conversion to 10 with concomitant isomerization to 9. The latter imine reacts slower in transfer hydrogenation. When starting from 9 the conversion to 10 is slower and the isomerization to 8 occurs at a much lower rate than that of isomerization of 8 to 9 (Scheme 10). This isomerization is likely to proceed through a ruthenium amine intermediate B. Unfortunately this intermediate could not be observed in an NMR experiment. Attempts to synthesize the corresponding ruthenium-amine complex were unsuccessful even though such complexes have been reported with primary amines and N-methyl amines. Casey and coworkers very recently reported a similar isomerization at -40 °C in a stoichiometric reaction with *N*-isopropyl-(*4-methyl)benzilideneamine and found a similar trend.

**Scheme 10. Isomerisation of imines 8 and 9.**

![Scheme 10. Isomerisation of imines 8 and 9.](image-url)

### 1.2.3 Ruthenium-amine complexes.

Ru-amine complexes are formed when the active species 6 is reacted with an imine. These Ru-amine complexes are unique for the hydrogenation of imines by 6. In the reaction of 6 with ketones (aldehydes) the products are the alcohol and the Shvo dimer 5 formed after A reacts with another hydride 6. To study the Ru-amine complexes which may play important roles as intermediates in catalysis we decided to form these complexes through the reaction of 6 with an imine. The experiments were run and analyzed by 1H NMR. Initially it was found that the complexes were formed and were stable at low temperatures, where for example imine 7 complexed with catalyst 6 at -40 °C and formed ruthenium-amine complex 11 (Scheme 11). At this temperature the complex was stable. However, when the temperature was increased to -30 °C, in the presence of 6, the complex
broke up and the free amine 12 and the dimeric Shvo catalyst 5 were visible in the \(^1\)H NMR in analogy with the reaction with benzaldehyde.

**Scheme 11.** Ru-amine complexes.

![Scheme 11](image)

It was found in the formation of the Ru-amine complexes that the electronic property of the imine correlates to the temperature at which the Ru-amine complexes were formed. When the benzyl group of the imine was substituted in the para position with a methoxy group the complexation started already at -58 °C. Substituting the N-phenyl group for a more electron-donating N-methyl group dramatically lowered the temperature for complexation to below -78 °C.

It was also found that the temperature at which these Ru-amine complexes decomposed to 5 and the free amine correlated to the electronic property of the amine formed. As mentioned above, Ru-amine complex 11 was stable to -30 °C in the presence of 6. The methoxy substituted analog was found to be stable to -25 °C. When the N-phenyl group was exchanged to an N-methyl group the corresponding complex, where both diastereomers were isolated by column chromatography, was stable to 47 °C in the presence of 6. Casey and coworkers have recently reported a similar study on aldimines and found the same pattern.35

**1.2.4 Kinetic isotope study.** To investigate if the hydrogen transfer comes into the rate expression, which suggests a concerted process, or if an alternative mechanism operates, it was decided to study the deuterium isotope effect for the transfer of hydride and proton from catalyst 6 to imine 13. If hydrogen transfer would be the rate-determining step this should show up in the isotope study.37 The observed rate constants for the formation of 14 (Scheme 12) was \( k_{\text{RuOH}} = (1.24 \pm 0.08) \times 10^{-3} \text{ s}^{-1} \) and for \( k_{\text{RuDOD}} = (1.18 \pm 0.09) \times 10^{-3} \text{ s}^{-1} \).38 The kinetic isotope effect calculated from the results is therefore \( k_{\text{RuOH}}/k_{\text{RuDOD}} = 1.05 \pm 0.14 \). The negligible isotope effect found for the hydrogenation of ketimine 13 therefore rules out the concerted mechanism proposed by Casey for this substrate.9a

Our group also found that the deuterium isotope effects for the reverse transfer dehydrogenation of N-phenyl-1-phenylethylamine 12 to the corresponding imine 7 were consistent with a stepwise mechanism.39 Thus, the combined isotope effect \( k_{\text{CHNH}}/k_{\text{CDND}} = 3.26 \) was equal to the individual isotope effect \( k_{\text{CHNH}}/k_{\text{CDNH}} = 3.24 \) and the other individual isotope effect \( k_{\text{NHCD}}/k_{\text{NDCD}} \) was very small.

This is in sharp contrast to the corresponding study on aldehydes9a where the kinetic isotope effect observed was \( k_{\text{RuOH}}/k_{\text{RuDOD}} = 3.6 \) which is in accordance with that the transfer of hydrogen from ruthenium and oxygen to the aldehyde occurs within the rate-determining step. Furthermore, the individual isotope effects were \( k_{\text{RuOH}}/k_{\text{RuDOH}} = 1.5 \) and \( k_{\text{RuOH}}/k_{\text{RuHOD}} = 2.2 \).
in accordance with a concerted process.\textsuperscript{40} Our group demonstrated that there is a simultaneous transfer of the two hydrogens in the reverse dehydrogenation of 1-(4-fluorophenyl)ethanol that gave a combined isotope effect of \( k_{\text{CHOH}}/k_{\text{CDOD}} = 4.61 \) and individual isotope effects \( k_{\text{CHOH}}/k_{\text{CHOD}} = 1.87 \) and \( k_{\text{CHOH}}/k_{\text{CDOH}} = 2.57 \), respectively.\textsuperscript{31}

**Scheme 12.** Kinetic isotope study of the hydrogenation of 13 to 14 by 6.

The results from the kinetic isotope studies clearly show the difference between the two substrate classes where the hydrogen transfer involving ketones (aldehydes) and alcohols is rate-determining and a concerted process whereas for the imines and amines it is not.\textsuperscript{41}

1.2.5 Exchange studies. To elucidate if the imine is coordinated to the catalyst during the hydrogen transfer, exchange studies were performed. In the concerted outer-sphere mechanism for the reaction of 6 with ketones (aldehydes), the substrate is not coordinated to 6 during the hydrogen transfer. When the hydrogen is transferred from 6 to the ketone (aldehyde) forming the alcohol, the ruthenium source converts to the reactive 16 electron complex A, which reacts with another molecule of 6 to form dimer 5.\textsuperscript{9a}

However, with the imines investigated the reaction is different and Ru-amine complexes are formed at low temperatures. If the outer-sphere mechanism were operating also for imines the reactive complex A formed would have to rapidly associate with the produced amine to give 15 to avoid the competing reaction of 6 with A to give dimer 5 (Scheme 13, Path A). However, if the imine coordinates to ruthenium prior to the hydrogen transfer forming intermediate C, the nitrogen would stay coordinated and give 15 without the presence of free complex A during the reaction (Scheme 13, Path B).

One way to distinguish between the two different pathways would be to have another similar amine present in equimolar amounts. In Path A the amine produced and the added amine would compete to associate with complex A. With a fast production of amine and A compared to association between the two (\( k_1 > k_2 \)), the ratio between the amine complexes 18 and 19 would be 1:1 (Scheme 14). With a slow production of the amine compared to the postulated association (\( k_1 < k_2 \)) the formation of the amine complex 19 (Ru-complex with added amine) would be larger than that of 18 (Ru-complex with amine produced) due to the in average larger concentration of the added amine 16 during the progress of the reaction. In path B there would be no incorporation of added amine in the amine complex (\( i.e. \) 19 should not be formed).
Scheme 13

Reaction of hydride complex 6 with the unsubstituted imine 17 in the presence of \( p \)-methoxy substituted amine 16 gave the amine complexes 18 and 19 in a ratio of 9:1 (Scheme 14).

Scheme 14. Exchange study.

The predominant formation of 18 (Scheme 14) provides strong support for Path B in Scheme 13 in which the imine is coordinated during the hydrogen transfer. The formation of complex 19 could in principle be explained by an outer-sphere mechanism.\(^9\) However, it would be expected that the relative amounts of 19 compared to 18 should be \( > 50\% \), in particular when taking into account that the more nucleophilic methoxy-substituted amine 16 should coordinate better to ruthenium than the unsubstituted amine formed \( \text{in situ} \) according to the mechanism proposed for ketones (aldehydes). The low ratio may be explained by a cage-effect where the amine formed by the hydrogenation is always in closer proximity to A than the added amine. If this is the case the ratio between 18 and 19 should be dependent on the concentration of the free amine in solution. The concentration dependence of the free amine 16 in the hydrogenation of 17 by 6 was therefore investigated. When using 0.5 equiv. of 16 the ratio between 18 and 19 had built up to 9:1. Using 1 equiv. of 16 the ratio between 18 and 19 was 9:1 after 5 minutes and was still 9:1 after 20 min. Even when 2 equiv. of 16 was used the ratio between 18 and 19 was 9:1 and the ratio was maintained after 20 min. The concentration of the amine
appears only to affect the rate of formation of 19 and not the ratio between the complexes 18 and 19.

Table 2. Concentration dependence in 16 for the formation of 19.

<table>
<thead>
<tr>
<th>equiv. of amine 16</th>
<th>time (min)</th>
<th>ratio of 18:19</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>5</td>
<td>98:2</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>9:1</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>9:1</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>9:1</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>9:1</td>
</tr>
</tbody>
</table>

The reactions were run at –20 °C using 0.1 mmol of 6 and 17 and varying the concentration of 16 in CD2Cl2. The reactions were analyzed by 1H NMR.

One explanation for the formation of 19 is that hydrogen gas is lost during the hydrogenation giving the active intermediate A and its dimeric form 20 as well as dimer 5 (Scheme 15) in a competing reaction. The free amine 16 in solution would then associate to either A or 20 and form 19. The ratio between these competing pathways would be independent of the amine concentration. To elucidate whether 19 was formed from the reaction of 16 and A or 20, the exchange study in Scheme 14 was run under H2 atmosphere, where H2 would quench A and 20 to give 6. No formation of 19 was observed in the presence of H2. Interestingly, the loss of hydrogen appears to be catalyzed by the imine. When 6 was mixed with the amine 16, neither 19 nor 5 were observed. Casey and coworkers have recently studied how substrates such as alcohols, phosphines, and even water promote the H2 elimination from 6.45

Scheme 15
These results indicate that the imine is coordinated to the catalyst either through a Ru-N bond or alternatively that the substrate is bound to another site of the catalyst during the hydrogen transfer.

1.3 Proposed mechanisms

Shvo originally proposed a mechanism where the ketone (aldehyde) coordinates to ruthenium in 6 followed by migratory insertion (Scheme 7). This mechanism was supported by the isolation of ruthenium-amine complexes. Casey and coworkers later showed that the hydrogen transfer for the reaction of 6' with benzaldehyde was concerted and proposed an outer-sphere mechanism for both ketones (aldehydes) and imines (Scheme 16) similar to the mechanism proposed by Noyori for catalyst 3 (Scheme 8), discussed in the introduction.

Scheme 16

We have proposed a mechanism where the catalyst equilibrates between η⁵ and η³ to generate a coordinately unsaturated species D (Scheme 17). The imine would coordinate to this η³ complex forming intermediate E. Hydrogen transfer is then rapid forming η² complex F, which then rearranges to η⁴ complex 15.

Scheme 17

Norton and Bullock have recently proposed an ionic mechanism for the hydrogenation of ketones (aldehydes) and imines by different transition metal catalysts. In this reaction the imine is activated through protonation prior to hydrogenation. The iminium cation can be formed either from protonation of the imine or alternatively a pyrrolidinium cation is used. The metal hydride is suggested to be delivered without prior coordination of the carbon-nitrogen double bond to produce a free amine and an unsaturated catalyst which can
form a complex with the amine. Even though the authors have not commented on the transformations involving the Shvo catalyst, their mechanism could be applied to the present system (Scheme 18). In the reaction with 6, the acidic OH would protonate the imine forming the iminium cation. Subsequent hydride addition of the iminium cation followed by coordination of the amine formed would give 15.

**Scheme 18**

![Scheme 18 Diagram]

Recently, Casey presented a modified mechanism for the hydrogen transfer of 6 to imines (Scheme 19). The hydrogen transfer is still concerted in this mechanism, but depending on whether the imine is electron-deficient or electron-rich the hydrogen transfer is rate-determining or not, respectively. In the latter case the coordination of the amine formed to the unsaturated ruthenium complex A is rate-determining (hydride shift from carbon to ruthenium competes with coordination).

**Scheme 19**

![Scheme 19 Diagram]

### 1.4 Mechanistic discussion

Casey’s first proposed mechanism, cannot account for the isotope effects found for the hydrogenation of imines nor the dehydrogenation of amines. The reactivity orders for imines > aldehydes and also ketimines > aldimines are also difficult to explain with an outer-sphere mechanism. The efficiency for the outer-sphere mechanisms is expected to correlate with the polarity of the double bond of the substrate. The results from the exchange studies are also difficult to explain with this mechanism.
Our initial mechanism based on Shvo’s proposal better explains the electronic effects observed where the stronger nucleophilicity of the substrate promotes the coordination. Also, the absence of isotope effect is adequately explained by this mechanism, where the coordination of the imine to ruthenium via ring-slippage is the rate-determining step and not the hydrogen transfer. Furthermore, this mechanism accounts for the results from the exchange studies where very little incorporation of free amine was observed and, more importantly, that this incorporation was independent of amine concentration.

Norton’s and Bullock’s ionic mechanism would account for the electronic effect of the substrate where electron-rich imines are better bases and thus deprotonates the hydroxyl group of 6 more efficiently. Supposing the hydride transfer is fast and reversible, this mechanism can explain both the isomerization where the β-elimination could occur from both sides of the nitrogen and the negligible isotope effect. This mechanism has problems explaining the exchange studies; however one can argue that the amine formed is in close proximity to the substrate by an interaction between the substrate and the catalyst.

Casey’s recently proposed mechanism for imines accounts for our observations including the electronic property of the imine, the isomerisation, the isotope effect and the exchange studies. However, the change of rate-determining step is somewhat contradictory. One would expect the reverse reactivity, namely that the hydrogen transfer is faster for an electron-deficient imine than for an electron-rich one, and that the formed amine would coordinate slower due to lower nucleophilicity. Also, this mechanism has problems to explain the isotope effect observed in the dehydrogenation of amines. According to the microscopic reversibility, the amine, after approaching \( \mathbf{A} \) (cf. Scheme 19) would undergo a concerted dehydrogenation. This is not observed; instead a stepwise hydrogen transfer occurs, where the C-H bond cleavage is rate determining.

For the ketimine we proposed an irreversible coordination step. For aldmines this step may be reversible and this modified version would account for the inverse isotope effect observed for some aldmines in the stoichiometric reaction. For an electron-rich ketimine the hydrogen transfer would be faster than the decoordination \((k_3 > k_2, \text{Scheme 17})\). For an electron-deficient imine the decoordination would be faster than hydrogen transfer \((k_2 > k_3, \text{Scheme 17})\). Our mechanism has been questioned on the basis of that no 13C labeled CO incorporation into complex 6 has been observed. Here we do not agree since the nucleophilicity of CO is very low and for coordination to occur a good nucleophile is required. Shvo has showed that ruthenium-amine complexes are very stable and does not exchange with a free amine in solution. It has even been found that CO exchange proceeds through a radical mechanism. However, we cannot exclude that the first step in our mechanism is an imine promoted \( \eta^5 \rightarrow \eta^3 \) ring-slippage. It is difficult to distinguish between a nucleophile-promoted ring slippage and a pre-equilibrium ring slippage.

Our mechanism, the ionic mechanism and Casey’s modified mechanism can all explain the experimental results presented in this chapter. The question arises whether the nitrogen of the imine is coordinated to ruthenium or bound to the ligand of the catalyst. This question will be very challenging to prove or disprove.
1.5 Conclusion

The results from this chapter clearly show the difference between the hydrogen transfer reactions involving carbonyls/alkohols and imines/amines and thereby questions the assumption of similarities in reactivity of these two substrate classes. We have found substrate effects where electron-rich imines give higher reaction rates than electron-deficient ones in various hydrogen transfer reactions. In the formation of Ru-amine complexes the electronic properties of the imine correlate with the temperature at which the complexation begins. Electron-rich imines form complexes with 6 at lower temperatures than electron-deficient imines. In the presence of 6 these complexes decompose into Shvo’s dimer 5 and the free amine. Also here the electronic property of the amine correlates with the temperature, at which the complexes decompose. Furthermore, the absence of kinetic isotope effect excludes a rate-determining hydrogen transfer in contrast to the reaction with ketones (aldehydes). We also conclude that the substrate is bound to the catalyst during the hydrogen transfer since in the exchange studies less than 10% incorporation of the free amine was observed. We have proposed a mechanism where the imine coordinates to ruthenium via an $\eta^5 \rightarrow \eta^3$ ring-slippage that would explain our results. However, Norton’s and Bullock’s ionic mechanism and Casey’s modified mechanism cannot be excluded.
2.1 Introduction

The first reduction of imines via transfer hydrogenation was reported by Grigg and coworkers in 1981. A rhodium catalyst was employed and only aldimines were investigated. Despite the importance of this discovery it took over a decade before this transformation got further studied. In 1992 our group reported the first ruthenium-catalyzed transfer hydrogenation of both ketimines and aldimines. Noyori and coworkers reported the first asymmetric version of this transformation in 1996. However, for this transformation a 5:2 formic acid-triethyl amine mixture was employed as hydrogen source, since 2-propanol did not work. Two years later Baker and coworkers reported the second asymmetric version, employing Noyori’s ligands to rhodium and using the same reaction conditions as Noyori. No asymmetric transfer hydrogenation of imines by 2-propanol has so far been reported. The lack of efficient procedures for transfer hydrogenation of imines by 2-propanol, motivated us to further study this reaction.

In the present work we have studied the catalytic transfer hydrogenation of imines employing active species \( \text{6} \) generated from different catalyst precursors. Species \( \text{6} \) hydrogenates the imine to the desired amine, and species \( \text{A} \) dehydrogenates 2-propanol to acetone (Scheme 20). In these processes complexes \( \text{6} \) and \( \text{A} \) are interconverted to one another. In this chapter the solvent effects, concentration dependence of 2-propanol, substrate effect of the imine, catalyst precursor, and the heating source are investigated for the transfer hydrogenation of imines to amines.

Scheme 20

2.2 Results and discussion

2.2.1 Preparation of starting materials. The imines were prepared from the corresponding carbonyl compound and amine. The reactions were carried out in the presence of molecular sieves with NaHCO₃ as base. The reactions proceed smoothly and in most cases the imines...
were isolated in good yields. Catalyst precursors 5 and 20 were prepared according to a literature procedure.\textsuperscript{9a}

2.2.2 Solvent effect. Since a dramatic solvent effect in the stoichiometric reaction of 6\textsuperscript{1} with benzaldehyde had been reported,\textsuperscript{9a} it was of interest to study the effect of an added cosolvent in the transfer hydrogenation of imines by 2-propanol. A preliminary screening indicated that benzene was an efficient cosolvent. In order to optimize the ratio between 2-propanol and cosolvent, we studied the rate of transfer hydrogenation of 7, with 5 as catalyst precursor, as a function of the concentration of 2-propanol in benzene (Figure 2). Surprisingly, the results show that the rate has a maximum, measured as initial TOF, at about 24 equivalents of 2-propanol to imine, which corresponds to a ratio benzene:2-propanol of 1.7:1. The concentration dependence is most likely due to two effects: at low concentrations of 2-propanol the rate-determining step is the generation of 6. This effect levels out at higher concentrations of 2-propanol and the negative solvent effect by 2-propanol compared to benzene will dominate, leading to a lower rate.\textsuperscript{43}

**Figure 2. Influence of 2-propanol on the rate**

![Figure 2](image)

\[ TOF = \text{Initial TOF} \]

\[ \text{Equivalents of 2-propanol to imine} \]

\[ a \text{ The reactions were run using imine 7 (0.3 mmol), catalyst 5 (0.9 µmol, 0.3 mol%), and benzene heated at 70 °C for 5 min. The equivalents of 2-propanol were varied (1-64 equivalents), preheated, and added.} \]

The effect of 2-propanol encouraged us to screen other cosolvents. Even though the optimal conditions for benzene perhaps would not account for other cosolvents we decided to use 24 equivalents of 2-propanol. The initial TOF h\textsuperscript{-1} as well as the conversion to amine after 90 min were measured. Toluene gave almost the same rate as benzene and both of these solvents gave full conversion to amine within 90 min (Table 3). Using more polar systems, such as THF,\textsuperscript{44} tert-butanol, or 2-propanol decreased the TOF h\textsuperscript{-1} and did not give full conversions after 90
min. For tert-butanol and THF this may be explained by a coordination of the solvent to A.\[^{44}\] However, for 2-propanol this should not lead to a rate deceleration since 2-propanol is expected to coordinate to ruthenium prior to dehydrogenation. A possible explanation for the rate deceleration for 2-propanol is that the precursor, the active species, the substrate, or another intermediate dissolves poorly. We observed a rate acceleration upon addition of small amounts of water (20\% rate acceleration with 0.8\% of water).\[^{9a,45}\]

### Table 3. Screening of different solvents.\[^{a}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>TOF[^{b}]</th>
<th>Conversion (%)[^{c}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>140</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>tert-Butanol</td>
<td>190</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>2-Propanol</td>
<td>250</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexane</td>
<td>440</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>650</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Benzene</td>
<td>700</td>
<td>100</td>
</tr>
</tbody>
</table>

\[^{a}\] These reactions were performed using catalyst 5 (2 \(\mu\)mol, 0.3 mol\%), imine 7 (0.6 mmol) dissolved in 2-propanol (1.1 mL, 14.4 mmol, 24 equiv.), and cosolvent (1.9 mL) at 70 °C. \[^{b}\] Measured after 10 min. \[^{c}\] Conversion after 90 min.

#### 2.2.3 Catalytic procedure.

The optimized conditions, \textit{i.e.} 24 equivalents of wet 2-propanol in benzene (2-propanol:benzene:H\(_2\)O = 1:1.7:0.02), were employed in the transfer hydrogenation of various imines. In most cases the reaction proceeds within a few hours at 70 °C using 0.3-1 mol\% of 5, giving excellent isolated yields. For example the imines 7, 13, 21, and 22 were isolated in 93-98\% yield after 0.75-1.5 h using 0.3 mol\% of catalyst (Table 4, entries 1-4). As stated in Part 1, electron-rich imines react faster than electron-deficient imines (Table 4, entries 1-5) and ketimines react faster than aldimines (Table 4, entries 1 and 7).\[^{46}\] This reactivity order is unusual and in contrast to the reactivity order usually observed for reduction of imines.\[^{47}\] Interestingly, this reaction seems to have high steric tolerance. For example the reaction was faster when the \(\alpha\)-methyl group was exchanged for an \(\alpha\)-ethyl group (Table 4, entries 1 and 3) and this is due to an electronic effect. Substituting the aromatic group with an aliphatic group decreased the rate (Table 4, entries 6, 8, and 9). Furthermore, very electron-deficient imines such as 28 gave poor results (Table 4, entry 10). The complete table is found in paper II.\[^{48}\]
### Table 4. Transfer hydrogenation of imines by 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Amine</th>
<th>C:S ratio</th>
<th>Time (min)</th>
<th>Yield $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhNPh</td>
<td>PhNPh</td>
<td>1:330</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>PMPNPh</td>
<td>PMPNPh</td>
<td>1:330</td>
<td>45</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>PhNPh</td>
<td>PhNPh</td>
<td>1:330</td>
<td>60</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>TolNPh</td>
<td>TolNPh</td>
<td>1:330</td>
<td>45</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>FPhNPh</td>
<td>FPhNPh</td>
<td>1:100</td>
<td>480</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>NPhNPh</td>
<td>NPhNPh</td>
<td>1:330</td>
<td>240</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>PhNPh</td>
<td>PhNPh</td>
<td>1:330</td>
<td>300</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>4NPh</td>
<td>4NPh</td>
<td>1:200</td>
<td>360</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>NPhPMP</td>
<td>NPhPMP</td>
<td>3:100</td>
<td>240</td>
<td>21$^c$</td>
</tr>
<tr>
<td>10</td>
<td>NPhPMP</td>
<td>NPhPMP</td>
<td>3:100</td>
<td>240</td>
<td>21$^c$</td>
</tr>
</tbody>
</table>

$^a$ The reactions were carried out using imine (1.0 mmol), 5 (0.003-0.01 mmol), and 2-propanol (24 mmol, 1.85 mL) in benzene (3.15 mL) at 70 °C. $^b$ Isolated yield. $^c$ NMR-yield. PMP = p-methoxyphenyl.

#### 2.3 Accelerating the reaction using microwave heating.

The use of microwave heating in organic synthesis dates back to the end of the 1980s when it was first found that microwave ovens could work as a heating source in chemical reactions. The pioneering work was conducted in domestic kitchen microwave ovens with poor control. Nowadays specialized equipment with controlled microwave heating is used. Microwave heating is convenient to use in organic synthesis. The heating is instantaneous, very specific and there is no contact required between the energy source and the reaction vessel reducing reaction times from hours to minutes. The use of microwaves to accelerate catalytic reactions
has recently attracted attention.\textsuperscript{50,51,52} In the literature there are only a few examples on the transfer hydrogenation.\textsuperscript{53} Employing microwaves reduce the reaction times considerably and this is of great use when a larger number of compounds are required (e.g. for screening).

We had found that microwave irradiation is superior to conventional oil bath heating for the generation of the active species 6 in a kinetic study (Part 1).\textsuperscript{1} Where conventional oil bath heating took several hours and without full conversion the microwave promoted generation of active species 6 from precursor 20 was very efficient. Active species 6 can be generated in a minute at 180 °C using microwave irradiation, but with somewhat irreproducible results.

We found that decreasing the temperature to 120 °C and prolonging the reaction time to 20 min generated 6 in total conversion and with full reproducibility (Scheme 21). We wanted to develop an efficient transfer hydrogenation for electron-deficient imines. Initially it was found that exchanging benzene for toluene and increasing the temperature to 110 °C in an oilbath gave promising results. This prompted us to investigate alternative heating sources where controlled microwave heating seemed appealing. In this chapter we have used microwave heating to lower the catalyst loading and reduce the reaction times in the ruthenium-catalyzed transfer hydrogenation of very electron-deficient functionalized imines to the corresponding amines.

Scheme 21

2.3.1 Choice of catalyst precursor. Even though both precursors 5 and 20 give 6, initial experiments revealed that they gave different rates in the transfer hydrogenation of imine 7. It was found that catalyst precursor 20 was more efficient than catalyst precursor 5. To obtain a more detailed comparison between the two catalyst precursors we studied their kinetics in transfer hydrogenation of imine 7. Thus, the transfer hydrogenation of imine 7 by 2-propanol-d\textsuperscript{8} in toluene-d\textsuperscript{8} catalyzed by 5 or 20 was monitored by \textsuperscript{1}H NMR at 70 °C. The results are shown in Figure 3. From these results it is evident that catalyst precursor 5 has an initiation period of several minutes, whereas catalyst precursor 20 is active immediately and gave a conversion of 23 % after 2 minutes. Because of the higher efficiency of 20 over 5 the former catalyst precursors was chosen for the further studies.
Comparison between pre-catalysts 5 and 20 in the transfer hydrogenation of imine 7 in toluene-d$_8$ at 70°C with 2-propanol-d$_8$ using 0.6 mol% catalyst. The conversion was measured by $^1$H NMR.

2.3.2 Catalytic procedure. Initial attempts to perform transfer hydrogenation with microwave irradiation gave unreliable results. For example when imine 7 was run with low catalyst loading (0.03-0.06 mol%) at 110 °C, the results were difficult to reproduce. Increasing the catalyst loading slightly (to 0.1 mol%) gave a smooth transfer hydrogenation of imine 7 to amine 12 within 20 min (Table 5, entry 1). Next it was of interest to find out if electron-deficient functionalized imines tolerate the transfer hydrogenation with microwave irradiation. The general trend was short reaction times (10-20 min) and low catalyst loading (0.1-0.5 mol%). Functional groups such as esters (Table 5, entries 2 and 3), acetals (Table 5, entry 5), ethers (Table 5, entry 4), and others (Table 5, entries 6 and 7) where successfully reduced. These substrates were not successfully transformed under oilbath conditions (70 °C) even at high catalyst loading after several hours. For example substrate 45 was not successfully transformed even with high catalyst loading (3 mol%) and long reaction time (Table 4, entry 10). Controlled microwave heating dramatically lowered the reaction time of 45 to 20 min giving 51 in 98% yield (Table 5, entry 7).
Table 5. Transfer hydrogenation of functionalized imines by 20 in wet 2-propanol-toluene using microwave irradiation.

\[
\begin{align*}
\text{Entry} & \quad \text{Imine} & \quad \text{Amine} & \quad \text{Catalyst loading (mol\%)} & \quad \text{Time (min)} & \quad \text{Yield}^b \\
1 & \text{Ph} & \text{Ph} & \text{COOMe} & \text{Ph} & \text{Ph} & \text{COOMe} & 0.1 & 20 & 98 \\
2 & \text{Ph} & \text{N-PMP} & \text{COOEt} & \text{Ph} & \text{N-PMP} & \text{COOEt} & 0.5 & 20 & 99 \\
3 & \text{N-PMP} & \text{N-PMP} & \text{COOEt} & \text{N-PMP} & \text{N-PMP} & \text{COOEt} & 0.3 & 20 & 93 \\
4 & \text{O} & \text{N-PMP} & \text{COOMe} & \text{O} & \text{N-PMP} & \text{COOMe} & 0.1 & 20 & 94 \\
5 & \text{MeO} & \text{O-Me} & \text{N-PMP} & \text{MeO} & \text{O-Me} & \text{N-PMP} & 0.5 & 10 & 98 \\
6 & \text{N-PMP} & \text{N-PMP} & \text{MeO} & \text{N-PMP} & \text{N-PMP} & \text{MeO} & 0.5 & 10 & 95 \\
7 & \text{N-PMP} & \text{N-PMP} & \text{MeO} & \text{N-PMP} & \text{N-PMP} & \text{MeO} & 3 & 20 & 98 \\
\end{align*}
\]

*The reactions were run using imine (0.3 mmol), 20 (0.3-9 µmol), and 2-propanol (1.1 mL) in toluene (1.9 mL), under microwave irradiation for 20 min (110 °C, ~2 bar). The yield was determined by $^1$H NMR. PMP = p-methoxyphenyl.

2.4 Conclusion

The transfer hydrogenation of imines using catalyst precursor 5 and 2-propanol shows an interesting solvent effect, where polar solvents decrease the rate. Less polar solvents with 24 equivalents of wet 2-propanol to imine showed a higher rate and the best solvent system (of those studied) were benzene and toluene. The substrate had a significant influence on the process. Ketimines react faster than aldimines. Electron-donating groups increase the rate while electron-withdrawing groups decrease the rate. The use of controlled microwave irradiation led to an efficient procedure where imines bearing labile functional groups, not compatible with conventional metal hydride reduction, can be readily reduced to the corresponding amines in >90 % yield within 20 min by employing 0.1-0.5 mol% of catalyst precursor 20.
Chapter 3 Transfer dehydrogenation of amines

3.1 Introduction

The oxidation of amines to imines is not a very common transformation. The most attractive way to transform amines to imines would be to selectively abstract a hydrogen molecule from the amine by a transition metal catalyst followed by oxidation of reduced metal or metal hydride complex with half an equivalent of oxygen, as the terminal oxidant. This would give water as the only waste. To accomplish this transformation there are many obstacles to overcome e.g. the usually high energy barrier for the reoxidation of the reduced form of the metal catalyst by molecular oxygen (see Scheme 3). James and coworkers reported the first aerobic oxidation of amines to imines in 1996 using a dioxo porphyrin-Ru complex. Recently Mizuno and coworkers reported an aerobic oxidation of primary amines to nitriles using Ru on Al₂O₃. In the latter report there were also some examples of the oxidation of secondary amines yielding aldimines. However, hydrolysis of the formed imine leading to low chemoselectivity was unfortunately problematic.

In addition to aerobic oxidation of amines to imines there are a few reports concerning related amine oxidations. In 1985 Murahashi and coworkers reported a catalytic procedure based on RuCl₂(PPh₃)₃ using tertbutylhydrogenperoxide as terminal oxidant that proceeds through a RuIV intermediate. The latter intermediate promoted the transformation of secondary amines to conjugated aldimines and cyclic ketimines. Other reports on the oxidation of amines to imines use a stoichiometric oxidant. For example, it was recently shown that ortho iodoxybenzoic acid (IBX) can transform amines to imines. Tetrapropylammonium perruthenate (TPAP) with N-morpholine (NMO) as final oxidant has also been reported. In addition to the high E factor in the use of a terminal oxidant other than molecular oxygen, there are drawbacks with all of these procedures. The substrate range is small. Both the efficiency and the chemoselectivity are problematic. Another problem is that the formed imines are very electrophilic and isolating them from the reaction media is complicated, especially when oxidants other than molecular oxygen are used.

In this chapter the oxidation of amines to imines is studied (Scheme 22). The catalyst, the substrate tolerance, and the terminal oxidants are investigated. The aerobic oxidation is also combined with organocatalysis in the generation of chiral amines.

Scheme 22. Coupled biomimetic oxidation of amines to imines using ETM:s
3.2 Results and discussion

3.2.1 Choice of catalyst. Because there are few reports on catalysts that promote transfer dehydrogenation of amines to imines it was decided from the principle of microscopic reversibility to initially screen catalysts that have been successfully reported for the transfer hydrogenation of imines to amines. The active species A can be generated from 5, 20, or from [Ph₄(η⁴-C₄CO)]Ru(CO)₃ (52) by loss of CO. We found that both complexes 5 and 20 showed a high activity in the transfer dehydrogenation of amine 56 using 2,6-dimethoxy-1,4-benzoquinone 53 as oxidant (Table 6, entries 1 and 2). However, complex 52 showed lower activity than catalysts 5 and 20 most likely due to the required CO dissociation from ruthenium being slow (Table 6, entry 3). Both Noyori’s catalyst (54) and RuCl₂(PPh₃)₃ (55), which have been successfully used in transfer hydrogenation of imines,⁹c,¹⁰a showed very low activity in the dehydrogenation (Table 6, entries 4 and 5).

Table 6. Catalyst screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield after 2 h %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuH</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Ru</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Ru</td>
<td>33c</td>
</tr>
<tr>
<td>4</td>
<td>Ru</td>
<td>10c,d</td>
</tr>
<tr>
<td>5</td>
<td>RuCl₂(PPh₃)₃</td>
<td>5c,d</td>
</tr>
</tbody>
</table>

a The reactions were carried out using amine (0.125 mmol), Ru-catalyst (2.5 µmol), quinone 53 (0.188 mmol) in toluene (1 ml) at 110 °C. b Determined by ¹H NMR spectroscopy. c The yield should be doubled because of the monomeric form of the pre-catalyst. d 4 mol% of K₂CO₃ was added.
3.2.2. Substrate effect on the Rate. In order to create an efficient oxidation of amines to imines we first wanted to investigate the substrate scope accepted by the catalyst and what the reaction rate depended on. We therefore studied the rate after 10 min and measured the conversion after 2 h. As mentioned in Part 1 the rate of all hydrogen transfer reactions of amines and imines were dependent on the electronic properties of the substrate. For example, substrates having a methoxy or a methyl group on one of the aromatic rings increased the rate (Table 7, entries 1-6). An additive effect was found when more than one methoxy group was introduced (Table 7, entry 1). In the transfer hydrogenation of imines we observed that aldimines react slower than ketimines. We observe the same trend for the reversed reaction studied here, dehydrogenation of amines, i.e. aldimines are generated slower than ketimines (Table 7, entry 9). In contrast to the transfer hydrogenation of imines an ethyl group instead of a methyl-group α to the amino-function did not increase the rate (Table 7, entry 8). A possible explanation is that the dehydrogenation is more sensitive towards steric effects than transfer hydrogenation. A p-CN substituent on the benzyl ring made the amine unreactive under the general conditions used. However, a high TOF was obtained using microwave assistance (Table 7, entry 10).
Table 7. Ruthenium-catalyzed dehydrogenation of amines to imines by quinone 53.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>TOF(^b) after 10 min h(^{-1})</th>
<th>Yield (%(^c)) after 1h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMP(^{58})</td>
<td>PMP(^7)</td>
<td>71</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td>Ph(^{59})</td>
<td>Ph(^{62})</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>Ph(^{60})</td>
<td>Ph(^{63})</td>
<td>58</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>PMP(^{30})</td>
<td>PMP(^{13})</td>
<td>51</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>Ph(^{56})</td>
<td>Ph(^{57})</td>
<td>47</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>Ph(^{12})</td>
<td>Ph(^{7})</td>
<td>33</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>Ph(^{33})</td>
<td>Ph(^{24})</td>
<td>32(^d)</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>Ph(^{29})</td>
<td>Ph(^{21})</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>Ph(^{34})</td>
<td>Ph(^{25})</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>NC(^{61})</td>
<td>NC(^{64})</td>
<td>&lt;1</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) The reactions were run using amine (0.125 mmol), 20 (2.5 µmol), and 53 (0.188 mmol) in toluene (1 ml) at 110 °C. \(^b\) TOF based on 20. \(^c\) Determined by \(^1\)H NMR spectroscopy. \(^d\) 4 mol% of 20 and 1.5 equiv. of quinone 53 was used. \(^e\) Run under microwave irradiation at 180 °C for 5 min. PMP = p-methoxyphenyl.

3.2.3 MnO\(_2\) as terminal oxidant. Our group has successfully reoxidized hydroquinones to benzoquinones by MnO\(_2\) in a ruthenium-catalyzed oxidation of alcohols.\(^58\) We therefore argued that MnO\(_2\) also would be compatible with the oxidation of 53, in the transfer dehydrogenation of amines. It was found that MnO\(_2\) worked as terminal oxidant for benzylic anilines that formed ketimines (Scheme 23). For example amines 58 and 59 were smoothly
transformed to the corresponding imines in high conversions (90 and 94%) within 4 hours. Despite that this was the first low-valent metal dehydrogenation of amines to the corresponding imines, the use of MnO₂ as terminal oxidant produces a lot of heavy metal waste leading to a high E factor and the need to purify the imine from the reaction mixture. This methodology was also restricted to aromatic benzyl anilines generating ketimines. Imines that required longer reaction times were hydrolyzed to the corresponding amine and carbonyl.

**Scheme 23**

3.2.4 Aerobic oxidation of amines. To develop an aerobic process for oxidation of amines to imines it is necessary to reoxidize hydroquinone 53b to quinone 53 with molecular oxygen. For the alcohol oxidation in biological systems, ubiquinol is reoxidized to ubiquinone with molecular oxygen activated by an iron porphyrin in cytochrome c. Recently, our group reported a successful coupled oxidation system of secondary alcohols that mimics this biological system where 53b was reoxidized by O₂ to generate 53. In this system a Co-salen type of complex (65) was found to be efficient in the activation of molecular oxygen (Figure 5).

**Figure 5.** Oxygen-activating catalyst 65.

It was of great interest to find out whether this artificial oxidation system also could be applied to the aerobic oxidation to amines. One concern was that the water formed could hydrolyze the imine, which was problematic in the previous study using MnO₂ as terminal oxidant, where substrates that required longer reaction times such as aldimines and substrates bearing a non-benzylic group underwent partial hydrolysis. Initial attempts to use the coupled aerobic system for oxidation of amines to imines gave varying results with difficulties to obtain good yields. After some variation of the reaction conditions we found that a moderate stream of air through the reaction flask gave the best results. A beneficial effect of this open system is that water formed under the reaction is removed. Thus, the biomimetic system used for alcohols works well also for the dehydrogenation of amines and generates the imines in good to high yields with catalytic amounts of 20, 53, and 65 under air (Table 8). Both ketimines (Table 8, entries 1-9) and aldimines (Table 8, entry 10) can be prepared from the corresponding amines.
Amines with a secondary alkyl group (which give ketimines) reacted faster than those with a primary alkyl group (which give aldimines). Interestingly, also nonbenzylic amines can be used as substrates with high selectivity (Table 8, entries 8 and 9). This is a nice example of how making a process more environmentally friendly also can result in an overall better system.

**Table 8.** Aerobic oxidation of amines using a biomimetic coupled catalytic system.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMP( \overset{\text{58}}{\text{N}} \overset{\text{H}}{\text{PMP}} )</td>
<td>PMP( \overset{\text{7}}{\text{N}} \overset{\text{H}}{\text{PMP}} )</td>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Ph( \overset{\text{59}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>Ph( \overset{\text{61}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>6</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>Ph( \overset{\text{60}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>Ph( \overset{\text{62}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>PMP( \overset{\text{30}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>PMP( \overset{\text{13}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>6</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>Ph( \overset{\text{56}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>Ph( \overset{\text{57}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>6</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Ph( \overset{\text{12}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>Ph( \overset{\text{7}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>Naphtyl( \overset{\text{63}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>Naphtyl( \overset{\text{66}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>12</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>( \overset{\text{33}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>( \overset{\text{24}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>12</td>
<td>83(^c)</td>
</tr>
<tr>
<td>9</td>
<td>( \overset{\text{64}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>( \overset{\text{67}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>12</td>
<td>76(^c,d)</td>
</tr>
<tr>
<td>10</td>
<td>( \overset{\text{34}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>( \overset{\text{25}}{\text{N}} \overset{\text{H}}{\text{Ph}} )</td>
<td>24</td>
<td>99(^c,e)</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise stated, the reactions were run using amine (0.125 mmol), 20 (2.5 \(\mu\)mol), 53 (25 \(\mu\)mol), and 65 (2.5 \(\mu\)mol), in 1 ml toluene at 110 °C under a steady flow of air. \(^b\) Determined by \(^1\)H NMR. \(^c\) 4 mol% of 20 was used. \(^d\) Traces of hydrolyzed product were observed in \(^1\)H NMR. PMP = \(p\)-methoxyphenyl.
3.2.5 Combining the aerobic oxidation with organocatalysis. As mentioned in the introduction, imines participate in a large number of synthetic transformations. The common way of preparing imines is from the corresponding carbonyl compound and the appropriate amine with removal of water under anhydrous conditions. The imine usually has to be isolated from this mixture before use in subsequent transformations. In the biomimetic catalytic aerobic oxidation of amines the imine is generated from the amine without any stoichiometric reagents except molecular oxygen. These conditions are favorable for using the imine in situ for further reactions. Here, we demonstrate that the imines generated from the aerobic oxidation procedure can be conveniently used in an organocatalytic reaction without further purification. Removal of the solvent from the aerobic oxidation reaction and replacing it with N-methyl-pyrrolidinone (NMP) followed by addition of L-proline and propionaldehyde gave syn-Mannich products in high yields and high ee:s. For example amine 77 was isolated in > 95% yield and in 99% ee (Table 9, entry 1). Substituting the amine in the para position with either electron-donating methoxy and methyl groups or with the electron-withdrawing group p-bromo led to slightly lower yields (Table 9, entries 3-5). These lower yields have been observed by others and a possible explanation is that these imines crystallize at -20 °C in the Mannich reaction. The benzyl group can be exchanged for an ester functionality even though longer reaction times and higher catalyst loading was required in the oxidation step for this very electron-deficient amine (Table 9, entry 8).
Table 9. Direct catalytic enantioselective addition of aldehydes to amines.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield\textsuperscript{b} (%)</th>
<th>dr\textsuperscript{c}</th>
<th>ee\textsuperscript{d} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhN\textsuperscript{PMP} 68</td>
<td>Ph\textsuperscript{PMP}OHN 77</td>
<td>&gt;95</td>
<td>19:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>NaphtylN\textsuperscript{PMP} 69</td>
<td>Naphtyl\textsuperscript{PMP}OHN 78</td>
<td>&gt;95</td>
<td>15:1</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>BrN\textsuperscript{PMP} 70</td>
<td>Br\textsuperscript{PMP}OHN 79</td>
<td>76</td>
<td>19:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>TolN\textsuperscript{PMP} 71</td>
<td>Tol\textsuperscript{PMP}OHN 80</td>
<td>75</td>
<td>8:1</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>PMPN\textsuperscript{PMP} 72</td>
<td>PMP\textsuperscript{PMP}OHN 81</td>
<td>63</td>
<td>10:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>N\textsuperscript{PMP} 73</td>
<td>N\textsuperscript{PMP}OHN 82</td>
<td>99</td>
<td>6:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>N\textsuperscript{PMP} 74</td>
<td>N\textsuperscript{PMP}OHN 83</td>
<td>&gt;95</td>
<td>19:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>EtOOCN\textsuperscript{PMP} 75</td>
<td>EtOOC\textsuperscript{PMP}OHN 84</td>
<td>&gt;95\textsuperscript{e}</td>
<td>19:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9</td>
<td>F\textsuperscript{PMP} 76</td>
<td>F\textsuperscript{PMP}OHN 85</td>
<td>&gt;95</td>
<td>15:1</td>
<td>99</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The reactions were run using amine (0.25 mmol), 20 (10 µmol), 53 (0.5 mmol), and 65 (5 µmol) in toluene (2 mL) at 110 °C for 24h. After the oxidation step, toluene was removed \textit{in vacuo}, NMP (1 mL) and L-proline (75 µmol) was added to the reaction flask, the temperature was decreased to -20 °C, propionaldehyde (0.75 mmol) was added, and the reaction was run for 16h.\textsuperscript{b} Isolated yields. \textsuperscript{c} Determined by NMR. \textsuperscript{d} Determined by chiral-phase HPLC analyses. \textsuperscript{e} 8 mol% of 20 and the oxidation was run for 72 h. PMP = p-methoxyphenyl.
3.3 Conclusion

We have developed an efficient catalytic process for oxidation of secondary amines that tolerates important substrate classes. The oxidation is based on the use of ruthenium complex 20, which works as substrate selective catalyst. The reduced form of this catalyst is then oxidized by the electron-rich quinone 53. The hydroquinone formed is then reoxidized to quinone by either MnO₂ or molecular oxygen. The latter reoxidation requires the presence of cobalt macrocycle 65, which activates O₂ and facilitates the electron transfer from hydroquinone to O₂. In the aerobic oxidation, both aldmines and ketimines can be prepared in good yields. Even unstable non-benzylic anilines were efficiently converted to imines without being hydrolyzed. The general trend is that electron-rich substrates react faster than electron-deficient substrates.

We have developed a new route to enantiomerically enriched amines by coupling the aerobic oxidation of amines with aldehydes in an organocatalytic Mannich reaction in one pot. Formally an amine is reacted with an aldehyde. The catalytic tandem reactions proceed with excellent chemoselectivity and enzyme-like selectivity, furnishing β-amino aldehydes in up to > 95% yield and > 99% ee.
Chapter 4. Racemization of amines

4.1 Introduction

Another attractive pathway to enantiomerically enriched amines is by resolution, of a racemic mixture with for example an enzyme. This process is named kinetic resolution where the enzyme has a higher activation barrier for reaction of one of the enantiomers, leading to different kinetics for the resolution of the two enantiomers. This system has the disadvantage of a maximum yield of 50%. To increase the yield, the configuration of the non- or slow-reacting enantiomer has to be inverted. An attractive way to increase the yield of the kinetic resolution is to apply an in situ racemization to the kinetic resolution, where the enantiomer that reacts slowly with the enzyme continuously is racemized. This process is called dynamic kinetic resolution (DKR) and has successfully been developed for alcohols in our group.\(^{64}\)

Although there are many reports on the kinetic resolution of amines, there are only few methods known in the literature for the racemization of amines.\(^{13,65}\) Moreover, their potential utility is hampered by their usually harsh reaction conditions (high temperatures, and strong basic and/or reductive media) making these procedures incompatible with several functional groups. Therefore, it is important to develop new methods to racemize amines under mild reaction conditions that can tolerate a wide number of different functional groups. Encouraged by our previous results from the hydrogen transfer reactions, we decided to study the racemization of chiral amines.

In this chapter the racemization of different amines and its combination with enzymatic kinetic resolution is studied.

4.2 Results and discussion

4.2.1 Side-product formation. In a first set of experiments the racemization of (S)-1-phenylethylamine ((S)-86) using Ru-catalyst precursor 5 was studied under different reaction conditions. The results are summarized in Table 10. Despite the complete racemization of (S)-86 (Table 10, entry 1), the efficiency of the process was poor, since considerable amounts of imine 87 and the corresponding amine 88 were formed via reductive elimination of the amino group (Scheme 24).

4.2.2 Reducing side-product formation. Several attempts to increase the efficiency of the process by reducing the amount of side-products have been carried out. Three different strategies were easily envisaged: a) dilution of the reaction mixture; b) addition of ammonia and c) addition of a hydrogen source to increase the concentration of 6.
Scheme 24

The results show that the concentration greatly affects the formation of side-products 87 and 88 (Table 10, entries 1-4). As expected, at low concentration the efficiency of the racemization was higher, but the side-product formation was not completely inhibited. The formation of side-products 87 and 88 could be effectively inhibited by the presence of ammonia (Table 10, entry 5). However, the scope of this procedure is limited since the use of highly basic ammonia reduces its functional group tolerance. Interestingly, we found that also the addition of 0.5 or 1 equivalents of 2,4-dimethyl-3-pentanol (89) as a mild hydrogen donor successfully inhibited the formation of side-products (Table 10, entries 6 and 7).

Table 10. Racemization of phenylethyl amine using catalyst precursor 5.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>t (h)</th>
<th>Additive (equiv.)</th>
<th>(86) (%)</th>
<th>(86) (ee)</th>
<th>(87) (%)</th>
<th>(88) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>-</td>
<td>1</td>
<td>5 (0)</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>-</td>
<td>0.5</td>
<td>21 (3)</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>-</td>
<td>0.25</td>
<td>84 (6)</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>-</td>
<td>0.125</td>
<td>91 (3)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>(\text{NH}_3) (1 atm)</td>
<td>0.25</td>
<td>98 (2)</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>0.5 equiv of 89</td>
<td>0.25</td>
<td>98 (2)</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: (S)-86 (0.25 mmol), 5 (5 mol%) in toluene at 100°C.

Another more problematic factor for side-product formation was water. When water was present side-product formation dominated. To avoid the side-products the reactions required completely dry conditions.

4.2.3 Substrate tolerance. A number of different amines were racemized employing this new procedure. Interestingly, both primary (Table 11, entries 1-4, 8-10) and secondary amines (Table 11, entries 5-7) were efficiently racemized under these conditions. A few functional groups were investigated. The \(\alpha\)-amino ester 95 was also efficiently racemized under these conditions (Table 11, entry 8). This method can also be applied to sterically hindered protected \(\alpha\)-amino alcohols 96 and 97. However, the efficiency of the process is lower. A possible explanation can be found in the high steric bulk of the silyl groups. This seems to be
corroborated by the higher efficiency when the phenyl groups of the TBDPS are replaced by the less hindered methyl groups (Table 11, entry 9 vs 10).

**Table 11.** Ru-catalyzed racemization of amines.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>%Racemization (1 h)b</th>
<th>Time (h)</th>
<th>amine (%) (%ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhN2</td>
<td>24</td>
<td>24</td>
<td>98 (3)</td>
</tr>
<tr>
<td>2</td>
<td>NH2F</td>
<td>21</td>
<td>24</td>
<td>95 (2)</td>
</tr>
<tr>
<td>3</td>
<td>NH2Tol</td>
<td>30</td>
<td>9</td>
<td>92 (2)</td>
</tr>
<tr>
<td>4</td>
<td>NH2Naphtyl</td>
<td>11</td>
<td>36</td>
<td>99 (5)</td>
</tr>
<tr>
<td>5</td>
<td>PhHN</td>
<td>100</td>
<td>1</td>
<td>&gt;99 (0)</td>
</tr>
<tr>
<td>6</td>
<td>HNPh</td>
<td>18</td>
<td>24</td>
<td>98 (1)</td>
</tr>
<tr>
<td>7</td>
<td>HNPh</td>
<td>44</td>
<td>12</td>
<td>&gt;99 (3)</td>
</tr>
<tr>
<td>8</td>
<td>PhCOOMe</td>
<td>28</td>
<td>12</td>
<td>98 (1)</td>
</tr>
<tr>
<td>9</td>
<td>NH2OTBDPS</td>
<td>-</td>
<td>48</td>
<td>&gt;95 (57)</td>
</tr>
<tr>
<td>10</td>
<td>NH2OTBDMS</td>
<td>-</td>
<td>48</td>
<td>&gt;95 (32)</td>
</tr>
</tbody>
</table>

*a Reactions were run using amine (0.25 mmol), 5 (5 mol%), and 89 (0.12 mmol) in toluene (2 mL). b % Racemization defined as 100-%ee, measured after 1 hour.

4.2.4 Combining racemization with kinetic resolution. As mentioned above the side-product formation was dependent on the amount of water present. When the DKR was attempted the side-products dominated. Perhaps the water dissolves the ammonia pushing the equilibrium towards 87 and 88. Therefore, the racemization procedure was combined with the
enzymatic kinetic resolution of primary amines in a two step manner (Scheme 25). The enantiomerically pure amides (S)-98 were efficiently prepared by enzymatic kinetic resolution using *Candida Antarctica* lipase (CALB) and ethyl acetate as acyl donor at 40 °C. After purification by extraction and distillation, the non-converted amine was racemized at 110 °C by 5 in the presence of 89. After the racemization, the recovered enzyme from the previous KR and ethyl acetate were added to the solution. After this second kinetic resolution run, the corresponding acetamide (R)-98 was isolated in good combined yield (69%) in almost enantiomerically pure form (ee > 98%).

**Scheme 25**

\[
\begin{align*}
\text{NH}_2 & \quad \text{CALB / AcOEt} \\
\text{toluene} & \quad \text{toluene} \\
\text{NHAc} & \quad 5, 89
\end{align*}
\]

4.3 Conclusion

We have developed an efficient procedure for the racemization of primary and secondary amines. Side-product formation is efficiently inhibited by running the racemization under dry conditions at low concentrations in the presence of a mild hydrogen donor. This process can be combined with the kinetic resolution in a two step procedure to yield primary amides in good yields in enantiomerically pure form (>98 % ee).
Concluding remarks

As the environmental awareness is awakening in chemistry, the demand for greener transformations is steadily increasing. The use of catalysts is an attractive approach to achieve these goals, especially if the catalyst can perform the reactions with the use of harmless chemicals.

We have studied a fairly undeveloped but very important catalytic transformation where a transition metal-based catalyst can selectively transfer hydrogen to and from imines and amines, respectively. More importantly, the catalyst works with harmless reductants and oxidants for this process under mild conditions. The hydrogen transfer has been studied in detail and synthetically useful applications have been developed.

The ruthenium-catalyzed hydrogen transfer involving amines and imines proceeds through a different route than anticipated from the studies involving alcohols and ketones (aldehydes).

The hydrogen transfer methodology can be used in several different transformations. The transfer hydrogenation of imines to amines can be carried out in either oil bath or by controlled microwave heating using 2-propanol as convenient hydrogen source. The yields are good to excellent. Even very labile imines were smoothly transformed to product using microwave heating.

The reverse transfer dehydrogenation of amines to imines was successfully performed. The hydroquinone formed from the reoxidation of the catalyst was shown to be oxidized back to benzoquinone by either MnO₂ or by molecular oxygen, where the latter oxidation requires a cobalt macrocycle as co-catalyst. The aerobic oxidation method gave an overall smoother oxidation process with broader substrate tolerance compared to the MnO₂ method. Another advantage with the green oxidation process is that although only oxygen is used as stoichiometric reagent and the water formed is continuously distilled off, there is no need to purify the imine prior to a subsequent reaction. This was demonstrated by the two step-one pot coupled process where the imines formed from the biomimetic oxidation were used without purification in a proline-based organocatalytic Mannich reaction giving, amino alcohols in high ee:s and yields.

The mild hydrogen transfer methodology was applied to the racemization of chiral amines. Interestingly, both primary and secondary amines were racemized with high efficiency.
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References

1. Amines can also be oxidized to nitroso compounds and hydroxylamines.
5. R. A. Sheldon, Pure Appl. Chem. 2000, 72, 1233.
32. TOF is determined as (mol substrate × conversion)/(mol catalyst × time).

33. Brune and coworkers observed an isomerisation with the Wilkinson catalyst see ref 9e.


36. Comparing the rate of the catalytic (paper II) and stoichiometric reaction (ref 35) and compensating for the catalytic amount of Ru-catalyst (paper II) and temperature, shows that the rate constants of the two isomerizations are of the same order of magnitude.


38. Six/seven different experiments were run for both RuHOH and RuDOD individually.


40. If the product of the individual isotope effects is close to combined isotope effect a concerted process is expected.

41. Casey and coworkers have also studied the isotope effect and found that very electron-deficient imines behave as aldehydes, see ref 35.


46. A more quantitative comparison of the electronic properties of the substrates is given in Part 1, Table 1 where the rate is measured as the initial TOF after 10 min.


54. These reactions were also run in an oilbath at 110 °C with good results. However, the reaction times were longer see paper III.


59. This overall redox reaction involves more detailed steps where the cytochrome first is reduced from FeIII to FeII followed by oxygen binding and another single electron transfer to generate Fe-OO-. This intermediate is then hydrolyzed to form water and the active FeV=O that subsequently oxidizes the substrate.


61. It was shown that 20 and 65 alone (without 53) slowly catalyzed the aerobic oxidation of amines to imines. After 1 h, < 10% conversion to imine was observed compared to > 30% with the coupled system. However, no oxidation took place without 20 (reaction checked after 4h).

62. For more examples of oxidation of amines giving aldimines see Table 9.
