Chapter 3

Asymmetric Transfer Hydrogenation of C=O and C=N Bonds Catalyzed by [Ru(η^6 arene)(diamine)] Complexes: A Multilateral Study

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Additional information is available at the end of the chapter

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Abstract

In these days, asymmetric transfer hydrogenation (ATH) is a very attractive method for synthesis of enantioenriched chiral compounds, especially fine chemicals such as drugs or agrochemicals. In this review, several topics related to the asymmetric transfer hydrogenation of ketones and cyclic or acyclic imines are discussed. Initially, the reaction mechanism of the ATH of ketones and imines, mainly 3,4-dihydroisoquinoline derivates, is examined. Next, typical reaction conditions, structural effects of the catalyst and a substrate, and analytical methods used for ATH monitoring and practical applications of the ATH in the chemical industry are described.

Keywords: ruthenium, asymmetric hydrogenation, imines, dihydroisoquinolines, catalysis

1. Introduction

Synthesis of biologically active chiral compounds such as drugs or pesticides goes hand in hand with the necessity of a high optical purity. Chiral molecules play an important role in many basic functions of living organisms, e.g., molecular recognition in biological systems is achieved by chiral environment (e.g., receptors), and thus the response induced by one enantiomer can be completely different from the other enantiomer of the same compound.

Commonly used synthetic approaches are not stereoselective and lead to a racemic mixture of the products from which the desired enantiomer is to be separated using specific separation methods, such as racemic cleavage. This method is relatively broadly applied in the chemical

industry but it can hardly be considered as ideal. Frequently, the yield of this process is limited only to 50% since the second (undesired) enantiomer is not recyclable and ends up as a waste. This fact represents a significant limitation, especially, during the synthesis of fine chemicals, e.g., drugs, where every loss can have a significant impact on profitability of the production process. These economical aspects are one of the most important reasons why the methods of enantioselective (asymmetric) synthesis are still in the forefront of modern synthetic chemistry.

From a historical point of view, the first described enantioselective reaction was asymmetric hydrogenation (AH). Mainly homogenous catalysts, represented by coordinated compounds with optically pure ligands, carrying asymmetric information, have been used in this type of reaction. These catalysts can be divided into several subgroups, e.g., according to the ligand structure, function groups, central atom, or mechanistic aspects. Nevertheless, the hydrogen source plays most prominent role. Meanwhile the classical asymmetric hydrogenation used gaseous hydrogen, while asymmetric transfer hydrogenation (ATH) focused on utilizing substances contained in the reaction mixture, such as propane-2-ol or azeotropic mixture of formic acid and triethylamine. The absence of gaseous hydrogen in the case of ATH enabled to skip the requirement of pressure reactors, which lowered the overall cost of the process and minimized the explosion hazard.

First, homogeneous catalysts to be applied in ATH of prochiral ketone and imine compounds were introduced by the group of professor Noyori between 1995 and 1996 [1, 2] (**Figure 1**). The catalysts contained ruthenium(II) as the central atom, enantioenriched chiral diamine ligand, such as *N* (2-amino-1,2-diphenylethyl)-4-toluenesulfonylamide, in short TsDPEN and η^6 aromatic ligand (e.g., benzene, *p*-cymene or mesitylene). The main advantage of these complexes lied in their high modularity. The structure of these complexes can be relatively easily modified in order to enhance their catalytic properties to better fit the hydrogenated substrate.

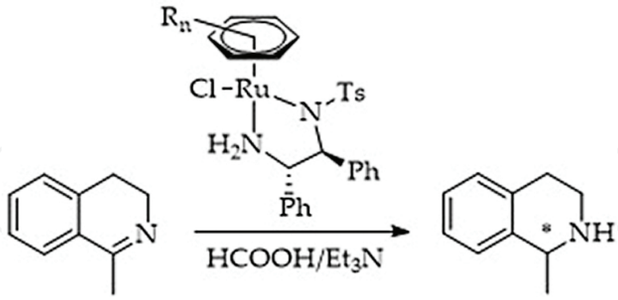

Figure 1. A scheme of asymmetric transfer hydrogenation of 1-methyl-3,4-dihydroisoquinoline.

This work is predominantly focused on the ATH of compounds with C=N and C=O double bonds in its structure using Noyori's ruthenium catalytic complexes. Additionally, several related topics are discussed such as the mechanism of asymmetric transfer hydrogenation of imines and ketones, the modification of the catalyst structure, the influence of the reaction conditions, and its application to the chemical industry and the synthesis of pharmaceutical substances.

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2. Mechanism of ATH catalyzed by [RuCl(η⁶-arene)TsDPEN]

The first study regarding mechanistic aspects of the reaction was performed by Noyori et al. in 2001 [3]. This work was focused on the ATH of ketones. By means of molecular modeling methods, it was demonstrated that the reaction proceeds *via* a six-membered cyclic transition state. For the purpose of these calculations, formaldehyde as the substrate and simplified structure of the catalytic complex, i.e., Ru(H)(η⁶-benzene)(ethylenediamine) were used (**Figure 2**). According to their findings, the substrate primarily formed C=O···H-N intermediate with the ruthenium complex and then evolved into six-membered cyclic transition state. Simultaneously, a proton transfer from the NH group took place to the carbonyl oxygen and hydride transfer onto the C=O carbon atom.

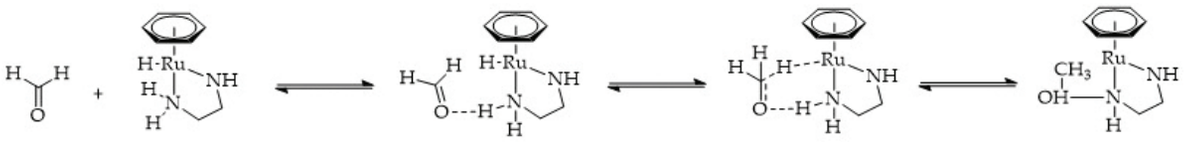

Figure 2. The original mechanistic concept published by Noyori et al. [3].

However, in 2013 Dub and Ikariya extended the previous Noyori's study and reported the detailed density functional theory (DFT) study [4], which showed that the hydrogenation of ketones occurred *via* a two-step pathway including the solvent as an important part of the hydrogen transfer mechanism.

From this perspective, the catalyst containing a ligand with (*S, S*) configuration provided (*S*) product. Nevertheless, Wills et al. [5] pointed out that this concept was not applicable on the ATH of imines, since the reaction was catalyzed by the catalyst with (*S, S*) configuration of the ligand providing (*R*)-product. An interesting fact was reported by Åberg et al. [6], who, in their study, proved that ATH of imines could be performed only in the presence of acids (for instance, an azeotropic mixture of formic acid and triethylamine), whereas ketones were possible to be hydrogenated also in alkaline medium. Imine, contrary to the ketone, enters the reaction in a protonated form and thus to perform the reaction itself, an acid addition is necessary. Consequently, Wills et al. [5] proposed several transition state structures, the so-called ionic mechanism, and presented their own experimental data.

2.1. Asymmetric transfer hydrogenation of cyclic imines (dihydroisoquinolines)

Theoretical work accompanied with the computational study with the application of DFT to investigate the ionic mechanism concept in ATH of 1-methyl-3,4-dihydroisoquinoline resulted in a series of interesting proposals. All calculations, having employed [Ru(Cl)(η⁶ *p* cymene)(*S, S)*-TsDPEN] as the catalyst, differentiated from the previous computational studies by the application of asymmetric η⁶-*p*-cymene ligand instead of typically used symmetric η⁶ benzene or η⁶ 1,2,3,4,5,6-hexamethylbenzene. The main outcome lied in the calculated structures of transition states, their energy minima followed by the construction of two energy diagrams

where the most probable structures have been studied. Furthermore, the resulting high enantioselectivity of the ATH of cyclic imines was explained.

It was assumed that a protonated substrate is attached to the molecule of the catalyst by the hydrogen bond between the hydrogen of the protonated substrate and the oxygen of the sulfonyl amide group of the catalyst and by that transition state is stabilized. Nonbinding interactions between π electrons of aromatic ring of the substrate and hydrogen atoms of *p*-cymene (i.e., CH/π interactions [7]), which also stabilize the favorable transition state, play a crucial role in the determination of enantiomeric excess (*ee*). Depending on energetic differences between "favorable" and "not favorable" transition states, geometry of the transition state determines *ee* of the product at the end of the reaction.

Besides, corresponding calculations allowed to suggest the pathway toward ATH of 1 methyl-3,4-dihydroisoquinoline using formic acid/triethylamine azeotrope as the source of hydrogen (**Figure 3**).

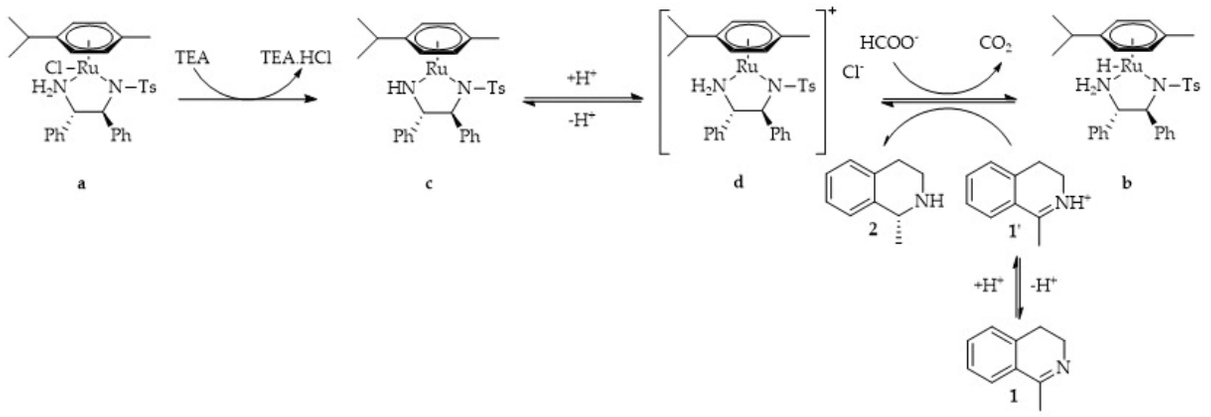

Figure 3. Suggested scheme of the catalytic cycle in ATH of 1-methyl-3,4 dihydroisoquinoline.

The proposed cycle starts with the transformation of the [Ru(Cl)(η^6 *p* cymene)(*S,S)* TsDPEN] complex (**a**) onto ruthenium-hydride (**b**), where this action is accompanied by the release of HCl, further neutralized by the present base (triethylamine), leading to the 16 ecomplex (**c**). In the next step, the complex (**c**) receives a proton from formic acid to form the complex (**d**), followed by the complex (**d**) turning in the presence of formate ion into ruthenium-hydride (**b**) and releasing CO_2. Finally, ruthenium-hydride participates in the asymmetric transfer hydrogenation process of the protonated substrate (**1'**). With the transfer of hydrogen from the complex (**b**) to the substrate (**1'**) the catalytic complex turns back to the intermediate (**d**). By this, the whole cycle is closed.

2.2. Asymmetric transfer hydrogenation of acyclic imines (*N*-benzyl-1-phenylethan-1-imin)

Asymmetric transfer hydrogenation of acyclic imines proceeds rather differently than in the case of cyclic imines such as substituted 3,4-dihydroisoquinolines. ATH of *N* benzyl-1-phenylethan-1-imin using Noyori's based catalyst with (*S, S*) ligand configuration lead to the

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excess of the product with (*S*)-configuration, which is in conflict with the results obtained in ATH of cyclic imines. The application of computational methods can help to find out [8] specific differences between both reaction types. It has been pointed out that in opposite to the rigid structure of cyclic imines, acyclic imines are very flexible in conformation and can undergo isomerization between *E* and *Z* isomer. Both of these isomers are capable of an interaction with the catalysts in a different way, ergo this fact has an extended impact on the enantioselectivity of the whole reaction, since both of the isomers are hydrogenated over different transition states. Therefore, in the case of the ATH of cyclic amines as well as in this case the transition state is stabilized by the hydrogen bond between the oxygen group of the catalyst and hydrogen of the protonated acyclic substrate. However, ATH of acyclic imines proceeds *via* the transition state with a different geometry producing the products with opposite geometry than in the case of cyclic imines such as 3,4-dihydroisoquinolines. Among other issues, this work stated that major *E* isomer is hydrogenated with a high selectivity to the corresponding (*S*)-isomer. Meanwhile, *Z* isomer is hydrogenated with much lower selectivity that causes decreasing of an overall enantioselectivity of the reaction.

2.3. Influence of the base on the asymmetric transfer hydrogenation of imines

To clarify the role of the base in asymmetric transfer hydrogenation of cyclic imines using Noyori's Ru(Cl)(η6-*p*-cymene)(*S,S)*-TsDPEN], catalyst is a rather complex problem [9]. The series of aliphatic (secondary, tertiary) or aromatic amines were employed into the formic acid/base system used for ATH. This work is divided into two parts, kinetic studies using *in situ* monitoring by nuclear magnetic resonance (NMR) spectroscopy and spectroscopic studies, including NMR spectroscopy, Fourier transform ion cyclotron resonance mass spectroscopy (FT-ICR MS), and vibrational circular dichroism (VCD) together with infrared (IR) spectroscopy. At first, during kinetic study of ATH of (*R*) 1,4 dimethyl-3,4-dihydroisoquinoline, substantially different reaction rates with various bases were observed. The highest reaction rates were measured after using tertiary bases, such as triethylamine (TEA), whose rate was over four times higher than *N, N* diisopropyl(ethyl)amine (DIPEA). Nevertheless, the secondary bases such as morpholine, piperidine, or pyrrolidine performed with even a lower reaction rate. Surprisingly, the reaction rate was rather high for aromatic amine, pyrrole and certainly low for pyridine. Both the reaction rate and asymmetric tendencies were significantly affected. In the case of diastereomeric excess (*de*), the lowest value was observed for DIPEA, followed by TEA. The secondary amines performed with a higher *de* over 60% and the highest value was obtained for pyrrolidine as one of the smallest molecules in the mixture. Also, *de* values for aromatic amines were in the range of 65–75%. These results suggested that differences in diastereoselectivity were triggered by the steric demands of the bases applied. A very similar procedure was performed using 1-methyl-3,4-dihydroisoquinoline as the substrate. As in the previous case, significant differences between additions of tertiary, secondary and aromatic bases were observed in terms of the reaction rate. Interestingly enough, a slightly higher reaction rate was observed using DIPEA, than TEA. However, the enantioselectivity was not significantly changed with the usage of various bases.

The spectroscopic methods were applied to understand the influence of the base in depth. For the NMR examinations, the mixture of [Ru(Cl)(η^6-*p*-cymene)(*S,S*)-TsDPEN] catalyst together with pure formic acid or the mixture of formic acid and TEA with different molar ratio were used. Employing pure formic acid was accompanied by the formation of the ruthenium-hydride species, which solely decomposed under acidic conditions. Furthermore, TEA addition has positive effect regarding the formation of catalytic hydride (**Figure 3**, complex **b**), positive effect was observed to the ratio of TEA/formic acid 5:1, and above this value no significant improvement in the case of hydride concentration was observed. Also, using ^{1}H-NMR spectrum, three intermediates were found in the mixture: (1) ruthenium-hydride species, (2) ruthenium formate complex [Ru($HCOO^-$)(η^6 *p* cymene)(*S,S*)-TsDPEN and (3) a species, which is assumed to be the second diastereomer of the ruthenium-hydride. After NMR experiments, ESI^+ FT-ICR MS to observe active ruthenium-hydride species using TEA/formic acid in molar ratio 5:2 was applied. The MS spectrum contained three clusters, the first one, with *m/z* 595.1500 which belonged to the 16 e^- complex (**Figure 3**, complex **c**), the second one, was determined as the cluster of active ruthenium-hydride associated with TEA. The last one, was assigned to the associate of a precatalyst (**Figure 3**, complex **a**) with TEA. From the results obtained, authors suggested that the binding of the base could be realized by three different ways: (1) the base is coordinated to the central Ru atom, (2) the base forms N···H-N bond with chiral ligand of the catalyst, or (3) the protonated base forms a N^+-H···O hydrogen bond with a sulfonyl group of the chiral ligand (**Figure 4**). To exactly determine which is the right way, the application of the VDC analytical method combined with IR spectroscopy concluded that the protonated base is connected with the catalytic complex *via* N^+-H···O hydrogen bond with a sulfonyl group of TsDPEN ligand. The consequence of these findings can be that the base selection has a huge impact on the reaction rate and enantioselectivity of the ATH of cyclic imines.

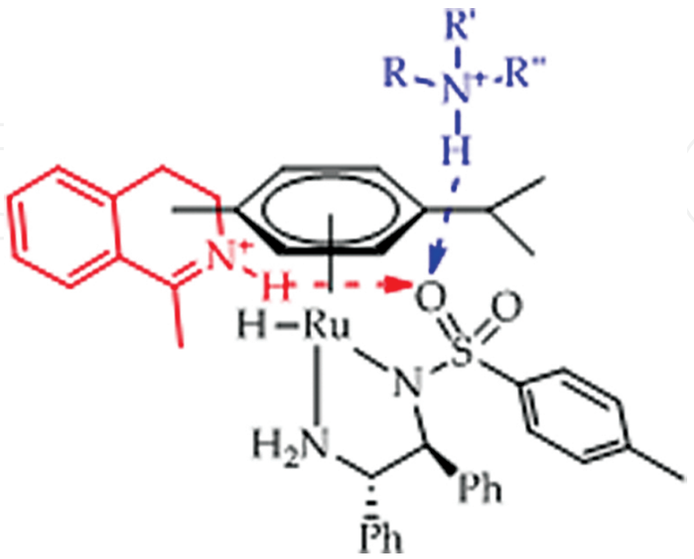

Figure 4. A scheme of binding of both substrate (red) and base (blue) to the active site of ruthenium-hydride species.

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3. Influence of the reaction conditions

Similar to every chemical reaction, it is important to carry out asymmetric transfer hydrogenation under specific reaction conditions, particularly ratio between the reaction rate and the enantioselectivity optimized as much as possible. The first comprehensive parametric study [10] focused on the determination of the best possible reaction conditions for ATH of cyclic imines, especially 3,4-dihydroisoquinoline derivates. This study thus involved clarifying the best attainable value of temperature, reaction mixture concentration or substrate to catalyst molar ratio (S/C).

Primarily, the attention was paid to the concentration in the reaction mixture as one of the important parameters. Two experiments were performed with different S/C molar ratios, S/C = 100 and S/C = 200, and other crucial molar ratios set to: formic acid/TEA = 2.5, hydrogenation mixture/substrate = 8.8, and the temperature set to 30°C. The major difference was observed in reaction ratio. For S/C = 200 the reaction ratio was slightly lower and also the difference grew with an increasing concentration. Probably, this fact can be explained by a certain amount of the catalyst being blocked by the protonated base, resulting in a lower reaction rate than in the case of the experiment with S/C = 100. The final outcome of this first set of experiments is as follows: reaction rate increases with an increasing of the reaction mixture concentration. This can be probably explained that at higher concentrations, the reaction rate is no longer limited by the frequency of effective collisions between active ruthenium-hydride species and the protonated molecule of the substrate but by the total amount of ruthenium-hydride intermediate present in the reaction mixture. Furthermore, the differences of the reaction mixture, related to the mass of the catalyst with different S/C ratios, were examined afterward as the S/C ratio is parameter that generally affects the course of catalytic reactions. As a result, it was confirmed that modifying S/C ratio leads to different reaction rates, regardless of the influence of the catalyst amount.

The second basic important parameter for every chemical reaction is the temperature. For this reaction, the measurement of its effect on both, the reaction rate and the enantioselectivity was conducted in the range of 10–50°C (**Figure 5**). Increasing the reaction rate with an increasing temperature was expected and could be considered common. However, the decrease of enantioselectivity was observed with an increasing temperature. This fact can be explained by Yamakawa's supported theory that two transition states exist. One would lead to the preferred configuration of the product; the other would lead to the other configuration. The so-called unfavorable transition state will prevail at a higher temperature and the nonpreferred product would become more abundant.

The amount of the hydrogenation mixture is also important for the process of ATH. The mixture of formic acid and TEA provides hydrogen for the hydrogenation itself. The most commonly used molar ratio for these two is 2:5. The variation of this amount was expected to have a major influence on the course of the reaction and thus several hydrogenation mixture/substrate ratios were tested, where the concentrations were set to 7%, as well as S/C = 100, formic acid/TEA = 2.5, and the temperature to 30°C. Contrary to the original expectation, increasing the amount of the hydrogenation mixture leads to a decrease in the initial reaction

rate (**Figure 5**). Therefore, two working hypothesis were considered to explain such behavior. The first, under a strong acidic condition, the catalyst's ligand became protonated, and subsequently deco-ordinated from the Ru atom, followed by the loss of catalytic activity and the second one, in a large excess of hydrogenation mixture, the protonated triethylamine is also in large excess over the protonated substrate and sterically hinders active site of the catalyst for substrate.

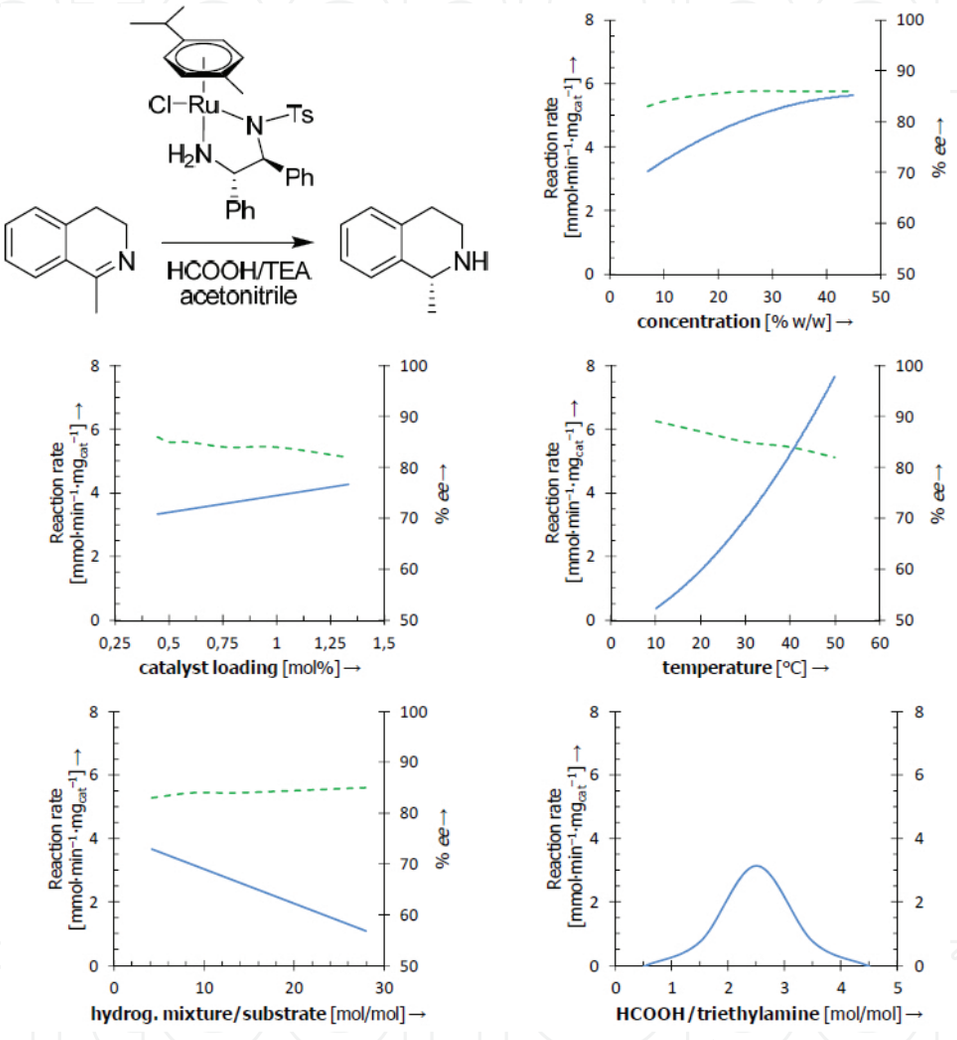

Figure 5. Graphical summary of the results obtained in parametric study of ATH.

The variation of the ratio between formic acid and triethylamine, the two components of the hydrogenation mixture, could provide an insight into several subtle aspects of the reaction mechanism. Also, several visual differences between reaction mixtures containing different molar ratios of TEA and formic acid were observed, yellow color for mixtures containing higher molar ratio between formic acid and triethylamine and orange color for the mixture with higher amount of base. This fact indicates that the catalytic complex undergo some significant changes in excess of acid followed by loss of activity of the catalyst. Although, using higher amount of the TEA also showed that the reaction perform much more slowly than usual.

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Explanation for this phenomenon could be really simple; the excess of TEA probably neutralizes all of the formic acid and by this disable the reaction itself. However, according to the results obtained during the study, azeotropic mixture of formic acid/TEA (molar ratio 5:2) seems to be an optimal as the source of hydrogen for the purpose of ATH (**Figure 5**).

4. Analytical methods tailored to asymmetric transfer hydrogenation

For the purpose of monitoring of the reaction and determination of *ee* of the reaction, several effective methods were developed. Kinetic study of hydrogenation can be realized in NMR spectrometer [11] and for the determination of *ee* method using derivatization of the sample followed by the determination of diastereoisomers using gas chromatography [12] can be applied.

4.1. *In situ* kinetic study using NMR spectroscopy

Implementation of the kinetic measurements of ATH of imines in flask brings some drawbacks. One of them is relatively complicated preparation of the sample for the following gas chromatography analysis. This preparation includes alkalinization of the reaction mixture for the release of the basic product and salt from formic acid, extraction of organic compounds into the diethyl ether, evaporating of the ether and dissolving of the sample with acetonitrile and analysis itself. For the practical reasons it is not possible to perform efficient enough kinetic measurements. To remove these drawbacks practical *in situ* NMR method of monitoring can be implemented. The core of this method lies in mixing of the catalyst together with the hydrogenation mixture (formic acid/TEA) dissolved in deuterated solvents like acetonitrile or dimethyl sulfoxide in NMR tube. The reaction is started by the addition of solution of substrate and in timely manner H^1-NMR spectra are acquired by automated software. By this, high-quality kinetic profile of the reaction is obtained without an intervention from the ambient environment.

4.2. Determination of the enantiomeric excess (*ee*) of ATH

Typical instrumental method for determination of optical purity at products of reaction is gas or liquid chromatography, using columns with chiral stationary phase. However, these columns are relatively expensive. Another disadvantage is that these columns is higher sensitivity, which manifest itself during GC analysis by lower temperature limit and at LC analysis by impossible analysis of any chemicals or are limited by certain pH. Hence, alternative methods using derivatization or chiral solvatation of the product are expedient.

4.2.1. Determination of ee by derivatization with (R)-menthyl-chloroformate

This method is based on a quantitative reaction of the product with (*R*)-menthyl-chloroformate. The result of the reaction is a mixture of two diastereomeric carbamates, which can be separated using gas chromatography without the necessity of using any chiral column. This

method was successfully validated and nowadays is used for the analysis of many tetrahydroisoquinoline derivatives with a sufficiently low boiling point to GC analysis.

4.2.2. Determination of ee by chiral solvation by Pirkle's alcohol

Chiral solvation by Pirkle's alcohol ((*R*)-(-)-1-(anthracen-9-yl)-2,2,2-trifluoroethanol) was used to determine *ee* at tetrahydroisoquinoline derivatives with a high boiling point. The method is based on the fact that the products of ATH provide diastereomeric solvates by the reaction with Pirkle's alcohol and each product can be distinguished by NMR analysis.

5. Structural effects of the catalyst and the cyclic imine substrate

The main result, regarding ATH of dihydroisoquinolines, depends either on individual structural fragments of the catalyst itself or substitution on the molecule of the substrate. Even a small change either in the structure of catalyst or substrate can have a significant impact on the enantioselectivity, reaction rate or even feasibility of the process.

5.1. Modification of the structure of Noyori's catalysts

As previously mentioned, one of the main advantages of Noyori's [Ru(Cl)(η^6 arene)(*S, S)* TsDPEN] catalysts is their structural flexibility. The structure of these complexes can be divided into three components, while each of them can be synthetically modified to increase the catalytic activity and enantioselectivity of the reaction in ATH of specific substrates (**Figure 6**).

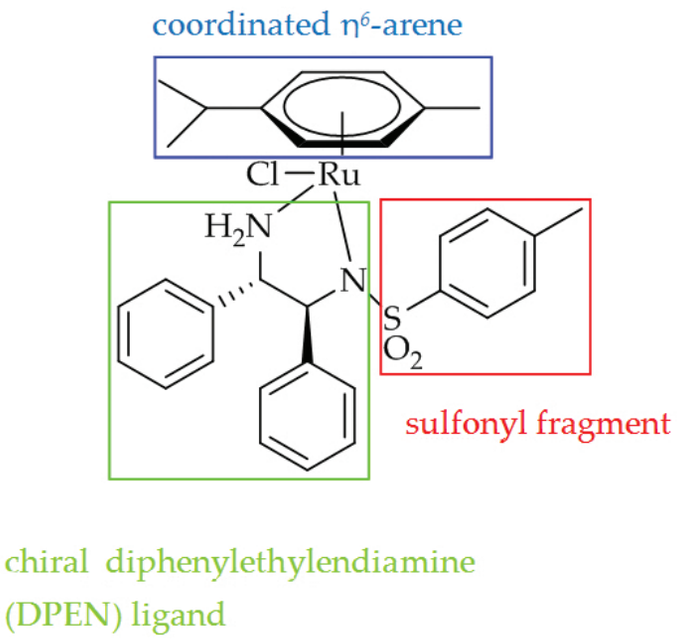

Figure 6. Scheme showing individual parts of the catalyst.

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5.1.1. Modification of the coordinated η⁶-arene

The core of enantioselectivity of asymmetric transfer hydrogenation lies in the weak bond between the hydrogen atom of η⁶-arene of the catalyst and π electrons of the aromatic ring of the substituted 3,4-dihydroisoquinoline substrate, e. g., CH/π interactions [7]. This interaction can assure the desired stabilization, providing the substrate molecule adopts a specific orientation permitting its formation. This interaction has also been one of the key reasons that gradually led to a certain abandoning of ketone-analogous mechanisms and formulations of the so-called ionic mechanism [5, 6, 13].

The work focused on the field of experimental testing of the Noyori based catalysts differentiated in their η⁶-arene in ATH of various substituted 3,4-dihydroisoquinolines, accompanied by a computational study [14]. For the evaluation of the effect of η⁶-arene ligand, a set of kinetic experiments was performed, followed by the determination of the enantiomeric purity of the products. For the purpose of this study, six cyclic imines (6, 7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 1-methyl-3,4-dihydroisoquinoline, 6 methoxy-1-methyl-3,4-dihydroisoquinoline, 7-methoxy-1-methyl-3,4-dihydroisoquinoline, 1-phenyl-3,4-dihydroisoquinoline, and 1-(4-trifluormethylphenyl)-3,4-dihydroisoquinoline) were tested in asymmetric transfer hydrogenation using four catalysts differing in their η⁶ arene ligand (*i.e.*, benzene, mesitylene, *p*-cymene and hexamethylbenzene). According to the results, catalysts bearing mesitylene and *p* cymene (**Figure 7**), could deliver higher *ee* values than the catalyst containing benzene as η⁶ arene ligand. The explanation of this fact was found out by authors during the molecular modeling. The calculation of transition states of the ATH with catalyst containing *p*-cymene and mesitylene suggested that for those two, it was possible to form a double CH/π interaction, whereas for the catalysts with a benzene ligand, only a single CH/π interaction could be formed that resulted in lower *ee* values.

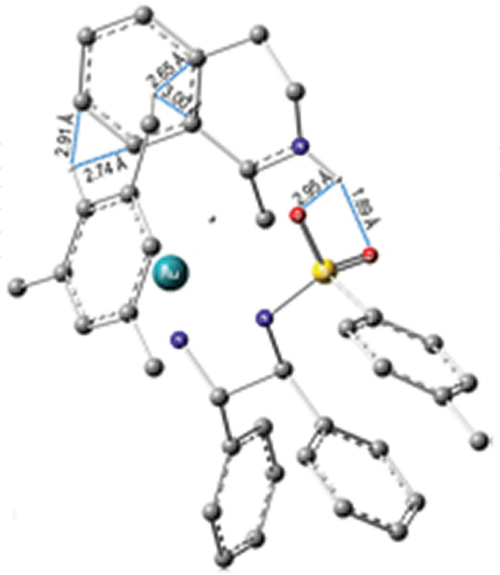

Figure 7. The so-called favorable transition state that occurred during the ATH of 1-methyl-3,4-dihydroisoquinoline.

Apart from the enantioselectivity, the modification of η^6-arene ligand affects also other reaction parameters. These include the turnover frequency (TOF), e.g., for the catalysts with hexamethylbenzene ligand, the TOF value was the smallest of all tested catalysts. Since homogeneous catalysis is involved, the solubility of the catalyst also plays a very important part of the synthesis. The modification of η^6-arene ligand significantly changes the solubility of the complex. The catalysts bearing mesitylene, *p* cymene and hexamethylbenzene were soluble in almost all polar solvents, whereas the catalyst with the benzene ligand was more or less soluble only in highly boiling solvents as dimethyl sulfoxide or *N*, *N* dimethylformamide.

5.1.2. Modification of the sulfonyl moiety

As mentioned in one of the previous sections, sulfonyl moiety of the catalyst, especially its oxygen atoms are important during the anticipated reaction mechanism where they serve as the active sites of the catalysts by interacting with both the protonated base and the protonated substrate with the use of hydrogen bonds. However, over a certain period of time, *N*-R-sulfonyl fragment was a target to a series of changes. Originally published catalysts [1, 2] contained *N*-aryl- or *N* alkylsulfonyl moieties of the TsDPEN ligand, typically mesityl (Mes), tosyl (Ts) or 1 naphthyl (Np). Later, the catalyst bearing methanesulfonyl fragment was found to be highly active in asymmetric hydrogenation of ketones and imines using gaseous hydrogen [15]. Among others, Wills and co-workers reported series of novel *N*-alkylated derivatives and tethered complexes, linking the arene and diamine ligand of the catalyst together [5, 16].

More profound modifications of *N*-R-sulfonyl fragment have been showed, aiming at substantial changes in catalyst's properties, e. g., for immobilization, or for conducting ATH in different media (water, ionic liquid, etc.) [17]. It is evident that the literature contains many interesting examples of structural variations. Nevertheless, the scope of available ligands is difficult to compare due to inconsistent reaction conditions.

5.1.2.1. Asymmetric transfer hydrogenation of 1-phenyl dihydroisoquinolines

Asymmetric transfer hydrogenation of 1-phenyl dihydroisoquinolines [18], represents a considerable challenge since the catalyst bearing the ligand of *N*-*p*-toluenesulfonyl-1, 2-diphenylethylenediamine (TsDPEN) failed to catalyze this reaction under standard reaction conditions. Although the original Noyori-type ATH catalysts always bore *N* arylsulfonyl as the substituent, several studies showed that Ir and Ru catalysts, containing methanesulfonyl-DPEN (MsDPEN), hydrogenated various aryl-*N*-benzyl imines, *N* sulfonylimines and aryl ketones with molecular hydrogen [5, 15, 19–21]. The ligand of methanesulfonyl DPEN is a part of a rather small group of ligands finding their use as a component of catalysts applicable for asymmetric (transfer) hydrogenation. Rather recently, another ligand bearing alkyl group, *N*-(camphor-10-sulfonyl)-DPEN (CsDPEN), was reported for its high efficiency in the ATH of a series of carbonyl compounds [22, 23]. However, no alkylsulfonyl diamines, such as 3,4 dihydroisoquinoline derivatives, have been applied in ATH of imines.

In addition, several Noyori-based Ru catalysts bearing *N*-naphtalene-1-sulfonyl-DPEN (NpsDPEN) and *N*-((*1S, 2S*-borneol-10-sulfonyl)-DPEN (CsDPEN) were tested in ATH of series of 1-phenyl-3,4-dihydroisoquinolines. The change of the original *N*-arylsulfonyl-DPEN from *p*-toluenesulfonyl-DPEN to naphthalene-1-sulfonyl in the catalysts structure, thus, enabled the catalytic activity in the ATH of aryl substituted 3,4-dihydroisoquinolines. The camphor fragment itself was indeed specific. The reaction which provided the desired catalytic complex was also an enantioselective reaction by itself. The preparation of the catalytic complex was performed in propane-2-ol, which also served as the hydrogen donor for ATH of ketones and thus the prepared complex also underwent transfer auto hydrogenation of the carbonyl group. The isolated crystalline material contained only one isomer. This isolated complex was tested in ATH of several 1-phenyl-3,4-dihydroisoquinolines derivates. Interestingly enough, in the reduction of aryl substrates containing electron-donating groups, the catalyst's performance was comparable with that measured with catalyst bearing naphthalene-1-sulfonyl-DPEN fragment. On the contrary, aryl substrates lacking electron-donating groups or even containing an electron withdrawing group displayed a very low catalytic activity. In the ATH of alkyl substrates, 1-methyl-3,4-dihydroisoquinoline and 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, the reactivity was much higher than with naphthalene-1-sulfonyl-DPEN, and slightly exceeding the activity of original Noyori's catalyst with toluenesulfonyl-DPEN ligand.

5.1.2.2. Comparison of the different sulfonyl moieties in the ATH of alkyl-3,4-dihydroisoquinolines

The role of sulfoonamide moiety of Noyori-based catalysts [Ru(II)Cl(η6 *p* cymene)(*S,S*)-(*N*-arylsulfonyl-DPEN) in the asymmetric transfer hydrogenation of two cyclic imine substrates (1-methyl-3,4-dihydroisoquinoline and 6,7 dimethoxy-1-methyl-3,4-dihydroisoquinoline) was also investigated [24]. All together, nine complexes, differing in substitution of the aromatic ring of the ligand, were synthesized and characterized, most of which have not been previously reported and the majority of the corresponding ligands have not been described in imine ATH.

As the standard, Noyori's original catalysts bearing N-*p*-toluenesulfonyl-DPEN ligand was selected, which served as the benchmark for the kinetic study. The substitution of the sulfonyl part of the catalyst was divided into several parts. The first were the ligands with bulky groups (*p*-(*tert*-butyl)phenyl, mesityl and 1-naphtyl), the second aromatic ring bearing electron donating methoxy groups differing in their position on the aromatic ring. Others were ligands with (3,4-dichloro)phenyl substituent as the representative of halogenated aromatic ring. The last two complexes contained: first, a very bulky and electron-poor 3,5-bis(trifluoromethyl)phenyl group, and the second, a heteroatom-containing ring, thiophene, chosen as an alternative to the common aromatic substituents.

The results obtained in this study showed that the change of aryl substituent on the sulfonyl part of the catalyst had a great influence on the reaction rate in ATH of 3,4 dihydroisoquinolines. Especially, the halogenated and hetero-aromatic substituents delivered reasonable reactivity only for one of the two substrates. The sterically demanding naphthyl containing ligand was the least preferred one.

5.2. Structural effects of the substrate

Isoquinoline-based molecules belong to the most important naturally-occurring alkaloids encompassing a significant group of biologically active species. These compounds have various pharmacological effects, which are enabled by their structural similarity with endogenous neurotransmitters. Therefore, a kinetic NMR study of ATH of five different 3,4 dihydroisoquinolines (**Figure 8**) was performed [25]. Four of them differed in various methoxy-substitutions of the dihydroisoquinoline skeleton, while the fifth examined substrate was a precursor for the production of mivacurium, a muscle relaxant. With 7 methoxy derivates (**3, 4, 5**), the reaction rate was significantly higher than in the case where no methoxy group was present in the position 7. The ATH of 6-methoxy-1-methyl-3,4-dihydroisoquinoline (**2**), bearing the 6-methoxy group, proceeded with a considerably lower reaction rate. However, the positive influence of the 7-methoxy group seemed to have overcome the detrimental effect of the 6-methoxy substituent when these two were present together, as it was for instance in the case of 6,7-dimethoxy-1-methyl-3,4-dihyroisoquinoline. Similarly, the bulky 1 (3′,4′,5′ trimethoxybenzyl) moiety of the last substrate (**5**) further enhanced the reaction performance.

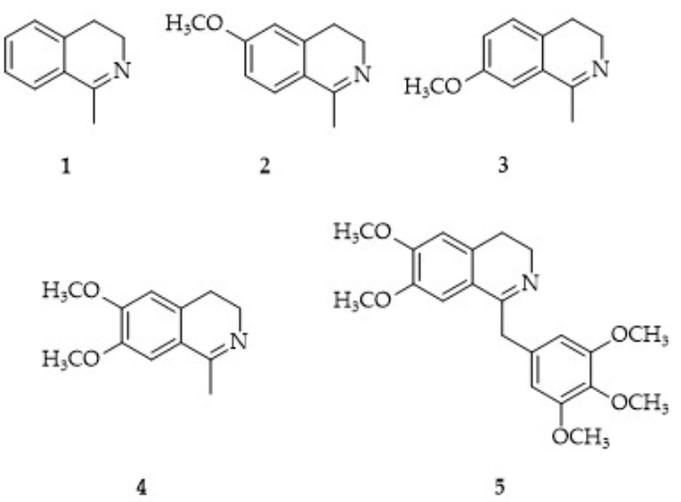

Figure 8. List of model substrates used to determine the effect of different substitution at the aromatic ring.

The substitution of the dihydroisoquinoline substrate with methoxy groups is followed by a much higher reaction rate and enantioselectivity than in the case of 1-methyl-3,4-dihydroisoquinoline (**1**). The presence of one methoxy group in the substrate molecule (**2** and **3**) led to an *ee* increase of 4–5 percentage points (89% (**2**) and 88% (**3**) versus 84% with the substrate **1**). With more methoxy groups affording *ees* higher by 9–10 percentage points (93% (**4**) and 94% (**5**) versus 84% with the substrate **1**). This observation could be attributed to substituent effects on the aromatic ring of the substrate, which affected the CH/π attraction between the catalyst and the substrate.

These experimental observations were supported by examining all involved substrates using molecular modeling, especially, the charge distribution (calculated Mulliken charges, NPA

http://dx.doi.org/10.5772/110623

charges and grid-based Bader analysis) on the C = N double bond (**Figure 9**). However, no expected correlations were found.

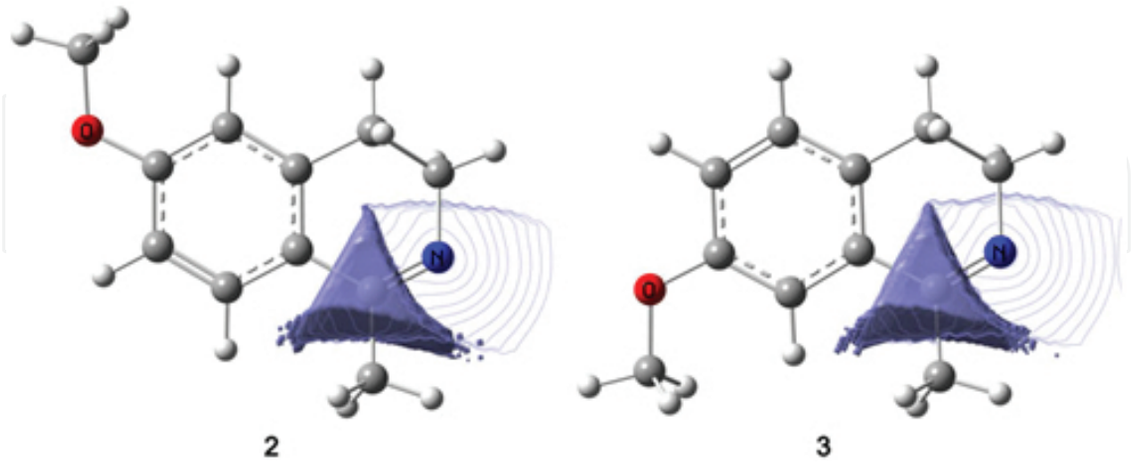

Figure 9. Partitions of total electron density on C and N atoms of imine bond of substrates containing one methoxy group.

To sum up, changing the position of single methoxy group resulted in drastic differences on the reaction performance in terms of both, the reaction rate and enantioselectivity. The presence of methoxy groups remarkably increased the reaction's enantioselectivity. Finally, an interesting conclusion could be drawn that less basic substrates were hydrogenated with higher reaction rates.

6. Practical industrial applications of asymmetric transfer hydrogenation

Even though asymmetric transfer hydrogenation was originally merely a subject of academic interest, nowadays this reaction finds its use also in several sectors of chemical industry. There are a large number of optically active amines and alcohols used as active substances and a suitable method for ATH preparation. As any method or technology, ATH inclusively has its pros and cons. The indisputable advantages, compared to asymmetric hydrogenation by gaseous hydrogen, are primarily the catalyst stability under air conditions (AH catalyst typically contains phosphine ligands, which easily undergo oxidation by atmospheric oxygen) and second, avoiding the use of gaseous hydrogen. These two facts actually permit testing many structurally different catalysts in a relatively short period of time. Eliminating the use of pressure hydrogen and thus the demanding apparatus for reactions at a high pressure noticeably simplifies the production facilities, which is an important aspect from the economical point of view.

Relatively small values of turnover frequencies (TOF) present one of the major drawbacks compared to AH catalysts. Extending the reaction time or using a higher amount of the catalyst represent potential solutions (since the catalysts for ATH are inexpensive compared to AH,

this solution is economically acceptable). Increasing the reaction temperature is, however, not the optimal solution, since enantioselectivity is decreasing with a higher temperature. Eliminating metal residues from the product is not an issue in these days as applying commercially available methods allows reducing the number of residues to units of *ppm*.

In 1997, Avencia Company patented rhodium catalysts bearing diamine, aminoalcohol ligands, respectively, for asymmetric transfer hydrogenation of imines and ketones. These Rh complexes are analogues to original Noyori's ruthenium catalysts. However, except for the central atom, these catalysts also differ in their aromatic ligand, which is in the most cases η^5-pentamethylcyclopentadienyl. These catalysts are used for the production of several different types of chiral alcohols and amines. To name some examples, one of the running processes is ATH of tetralone to (*R*)-1-tetralol with the capacity of 200 dm^3 and the corresponding yield of 95 and 97% *ee*, than the process of preparation of (*S*)-1-(4-flurophenyl)ethanol with its yield of 85 and 98.4% *ee* or the production of (*R*)-N-diphenylphosphinyl-1-methylamine with 95% yield and 99% *ee* [26].

Asymmetric transfer hydrogenation has the potential to find use also in the production of fine chemicals such as drugs, where a high optical purity of the final products is demanded. To provide an example, the preparation of the precursor for the synthesis of muscle relaxant, mivacurium-chloride, can be mentioned [27]. In this case, the application of ATH for the preparation of mivacurium-chloride seems to be a more favorable, since the cleavage used in the classical preparation, capitalizing on using *L*-dibenzoyltartaric acid to separate both enantiomers, is rather ineffective and produce a lot of nonrecyclable waste.

7. Conclusion

The main purpose of this study was to describe selected parts of the asymmetric transfer hydrogenation of ketones and particularly imines. Our attention was predominantly aimed to the importance of the mechanistic aspects of the ATH or structural effects influencing the reaction course. All parts of this work show that the asymmetric transfer hydrogenation is the reaction which can find its use across all branches of the chemical industry.

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