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Asymmetric transfer hydrogenation of ketones

Catalyst development and mechanistic investigation

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Cover picture: White wagtail by Katrin Ahlford

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Den rechten Weg wirst nie vermissen,
Handle nur nach Gefühl und Gewissen.

Johann Wolfgang von Goethe,
Zahme Xenien

Abstract

The development of ligands derived from natural amino acids for asymmetric transfer hydrogenation (ATH) of prochiral ketones is described herein. In the first part, reductions performed in alcoholic media are examined, where it is found that amino acid-derived hydroxamic acids and thioamides, respectively, are simple and versatile ligands that in combination with $[RhCp^*Cl_2]_2$ efficiently catalyze this particular transformation. Selectivities up to 97% ee of the corresponding secondary alcohols are obtained, and it is furthermore observed that the two different ligand classes, albeit based on the same amino acid scaffold, give rise to products of opposite configuration.

The highly interesting enantioswitchable nature of the two abovementioned catalysts is studied in detail by mechanistic investigations. A structure/activity correlation analysis is performed, which reveals that the diverse behavior of the catalysts arise from different interactions between the ligands and the metal. Kinetic studies furthermore stress the catalyst divergence, since a difference in the rate determining step is established from initial rate measurements. In addition, rate constants are determined for each step of the overall reduction process.

In the last part, catalyst development for ATH executed in water is discussed. The applicability of hydroxamic acid ligands is further extended, and catalysts based on these compounds are found to be efficient and compatible with aqueous conditions. The structurally even simpler amino acid amide is also evaluated as a ligand, and selectivities up to 90% ee are obtained in the reduction of a number of aryl alkyl ketones. The very challenging reduction of dialkyl ketones is moreover examined in the Rh-catalyzed aqueous ATH, where a modified surfactant-resembling sulfonylated diamine is used as ligand, and the reaction is carried out in the presence of SDS-micelles. A positive effect is to some extent found on the catalyst performance upon addition of phase-transfer components, especially regarding the catalytic activity in the reduction of more hydrophobic substrates.

List of publications

The thesis is based on the following publications, which will be referred to by Roman numerals. Reprints were made with permission from the publishers (see appendix I). The contribution by the author to each publication is clarified in appendix II.

I **A simple and efficient catalyst system for the asymmetric transfer hydrogenation of ketones**
Katrin Ahlford, Alexey B. Zaitsev, Jesper Ekström, Hans Adolfsson
Synlett **2007**, 2541-2544

II **Fine-tuning catalytic activity and selectivity - [Rh(amino acid thioamide)] complexes for efficient ketone reduction**
Katrin Ahlford, Madeleine Livendahl, Hans Adolfsson
Tetrahedron Letters **2009**, *50*, 6321-6324

III **Asymmetric transfer hydrogenation of ketones catalyzed by amino acid-derived rhodium complexes: on the origin of enantioselectivity and enantioswitchability**
Katrin Ahlford, Jesper Ekström, Alexey B. Zaitsev, Per Ryberg, Lars Eriksson, Hans Adolfsson
Chemistry – A European Journal **2009**, *15*, 11197-11209

IV **Amino acid-derived amides and hydroxamic acids as ligands for asymmetric transfer hydrogenation in aqueous media**
Katrin Ahlford, Hans Adolfsson
Catalysis Communications **2011**, in press

V **Rhodium-catalyzed asymmetric transfer hydrogenation of alkyl and aryl ketones in aqueous media**
Katrin Ahlford, Jesper Lind, Lena Mäler, Hans Adolfsson
Green Chemistry **2008**, *10*, 832-835

Contents

1. Introduction

Extensive research is going on in the field of medicinal chemistry, not only to find new biologically active compounds, but also to improve reaction procedures that can lower costs and produce less waste. Traditionally, organic reactions often involve stoichiometric amounts of reagents. However, it has become important to find reactions where substoichiometric amounts can be utilized. Acid and base catalysis have been used to trigger reactions for centuries, nevertheless, a variety of more sophisticated catalytic systems is nowadays available. Catalysis can be categorized as homogeneous and heterogeneous, where an important and popular example of the former is metal catalysis.[1]

If an organic molecule contains a carbon atom substituted with four different groups, the carbon is a stereogenic center and the molecule is referred to as chiral. The principle behind asymmetry is the fact that two different spatial arrangements of the groups in a stereocenter are possible, giving so-called enantiomers, which are each other's non-superimposable mirror images.[2] One of nature's own examples of a chiral molecule is the amino acids, where normally only one enantiomer is available in nature and the other enantiomer must be prepared synthetically. Chirality is illustrated with the two enantiomers of the amino acid valine and the human hands in Figure 1.

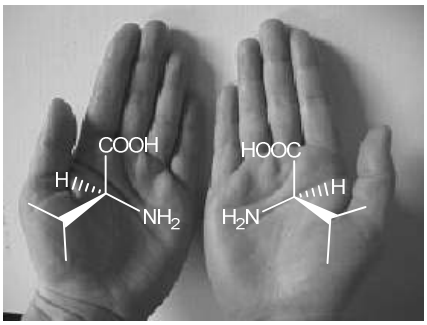


Figure 1. The enantiomers of the amino acid valine (*S* left and *R* right).

[1] Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, University Science Books, Sausalito, California, **2006**, p. 490.
[2] Eliel, E. L.; Wilen, S. H. *Stereochemistry of organic compounds*, John Wiley & Sons, Inc., New York, **1994**, p. 4.

The enantiomers of a chiral compound, e.g. a pharmaceutical, can have completely different behavior when interacting with a chiral environment, such as the human body, which could be beneficial, but in some cases even dangerous. Another possible scenario is where one isomer can interact with the body, while the other isomer is completely inactive. The awareness of nature's handedness has increased the preparation of compounds with defined stereochemistry, since many of the produced pharmaceuticals of interest contain one or several stereogenic centers.[3] It is essential to study all possible isomers of a potential drug, and it is thus important to develop asymmetric protocols for fundamental building blocks employed in the synthesis of pharmaceuticals. To emphasize the importance of asymmetry in medicinal chemistry, 80% of all pharmaceuticals on the market in 2006 were chiral molecules, 75% of which were single enantiomers.[4]

The reduction of unsaturated compounds can introduce new functionalities in an organic molecule. Depending on the substrate and the reagents used, chirality can simultaneously be introduced.[5] Many biologically active compounds, along with important building blocks of the pharmaceutical industry, have stereogenic centers containing hydrogen and an alcohol functionality.[6] The field of asymmetric reductions has thus not surprisingly been widely explored. A convenient method for obtaining chiral secondary alcohols is the enantioselective reduction of prochiral ketones, which can be achieved by metal catalysis using enantiomerically pure complexes. Two different approaches can be utilized to perform this transformation, either direct hydrogenation using molecular hydrogen, or via hydrogen transfer from a suitable donor molecule.[7] Alkenes are easily reduced via direct hydrogenation, whereas unsaturated compounds involving heteroatoms (e.g. ketones or imines) are often reduced by the latter method. Hydrogen transfer reductions have become more popular in recent years, mainly due to the avoidance of hazardous reagents,[8] and hence, the aim of the thesis is to study and develop this reaction further.

1.1 Transfer hydrogenation

The first examples of hydrogen transfer from an alcohol to a ketone were reported by Meerwein, Verley and Ponndorf (MPV-reaction), respectively,

[3] Caner, H.; Groner, E.; Levy, L.; Agranat, I. *Drug Discov. Today* **2004**, *9*, 105.
[4] *Chemical & Engineering News* **2007**, *85*, 11.
[5] Andersson, P. G.; Munslow, I. J. Eds. *Modern Reduction Methods,* Wiley-VCH, Weinheim, **2008**.
[6] Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev*. **2006,** *106*, 2734.
[7] Samec, J. S. M.; Bäckvall, J-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237.
[8] Wu, X.; Xiao, J. *Chem. Commun.* **2007**, 2449.

in the mid 1920's.[9] The use of a stoichiometric amount of aluminum isopropoxide allowed for hydrogen transfer from 2-propanol to a ketone, forming a secondary alcohol and acetone. In 1937 Oppenauer described the oxidation of secondary alcohols in steroids to the corresponding ketones using aluminum *tert*-butoxide and acetone as the hydride acceptor,[10] which proves the reversibility of the reaction. The equilibrium can be shifted to the desired product depending on having a large excess of either 2-propanol or acetone, preferentially as the solvent.

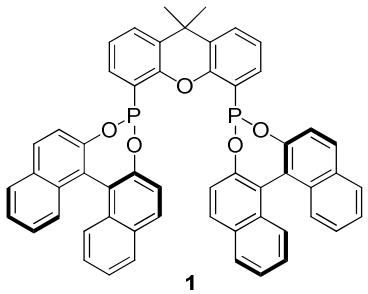
The first example of a transition metal-catalyzed transfer hydrogenation, employing an Ir-DMSO-complex, was presented in 1967 by Henbest.[11] Some years later, the first efficient Ru-catalyzed transfer hydrogenation was reported.[12] An important discovery was made by Bäckvall and Chowdhury in 1991, when a dramatic rate acceleration was achieved upon addition of base to the reaction mixture using $RuCl_2(PPh_3)_3$ as the catalyst.[13] The use of less precious metal sources is evidently highly desirable and recently, iron-based catalysts showing useful activity and selectivity in hydrogen transfer reactions were reported for the first time.[14]

1.1.1 Asymmetric transfer hydrogenation

Asymmetric transfer hydrogenation (ATH) can be defined as "the reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst".[15] The chiral catalysts used in this reaction most often consist of a transition metal ion in combination with chiral ligands.[16] However, in recent years, simple organic chiral catalysts have also been used for this particular transformation.[17] Among the most active and selective catalysts reported so far are those containing the ligands diphosphonite **1**,[18] pyridine derivative **2**,[19] amino alcohol **3**[20] and aza-norbornyl

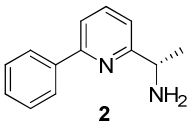
[9] a) Meerwein, H.; Schmidt, R. *Justus Liebigs Ann. Chem.* **1925**, *444*, 221; b) Verley, A. *Bull. Soc. Fr.* **1925**, *37*, 537; c) Ponndorf, W. *Angew. Chem.* **1926**, *39*, 138.
[10] Oppenauer, R. V. *Recl. Trav. Chim. Pays-Bas.* **1937**, *56*, 137.
[11] Trocha-Grimshaw, J.; Henbest, H. B. *Chem. Commun.* **1967**, 544.
[12] a) Sasson, Y.; Blum, J. *Tetrahedron Lett.* **1971**, 2167; b) Sasson, Y.; Blum, J. *J. Org. Chem.* **1975**, *40*, 1887.
[13] Chowdhury, R. L.; Bäckvall, J-E. *Chem. Commun.* **1991**, 1063.
[14] a) Zhou, S.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8121; b) Mikhailine, A. A.; Morris, R. H. *Inorg. Chem.* **2010**, *49*, 11039; c) Naik, A.; Maji, T.; Reiser, O. *Chem. Commun.* **2010**, *46*, 4475; d) Meyer, N.; Lough, A. L.; Morris, R. H. *Chem. Eur. J.* **2009**, *15*, 5605; e) Mikhailine, A.; Lough, A. L.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1394.
[15] Wu, X.; Wang, C.; Xiao, J. *Platinum Metals Rev.* **2010**, *54,* 3.
[16] a) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226; b) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.
[17] Adolfsson H. in *Modern Reduction Methods*; Andersson, P. G.; Munslow, I. J. Eds.; Wiley-VCH, Weinheim, **2008**, p. 341.
[18] Reetz, M. T.; Li, X. *J. Am. Chem. Soc.* **2006**, *128*, 1044.

alcohol **4**,[21] as well as complexes **5**[22] and **6**,[23] which are based on monotosylated diamine ligands.



1

Bidentate phosphorus donor ligands generally work better in enantioselective hydrogenation reactions than in asymmetric hydrogen transfer reactions. An exception is ligand **1**, which has a large bite angle and generates a highly efficient and selective catalyst for ketone reductions under transfer hydrogenation conditions when used together with $[Ru(p\text{-cymene})Cl_2]_2$.[18,24]



2

The pyridine-derived ligand **2** binds in a pincer-type fashion when coordinated to $[RuCl_2(PPh_3)_3]$. When this complex is combined with a chiral diphosphine ligand, the catalyst formed shows astonishingly high turnover frequencies at loadings as low as 0.005 mol%.[19]

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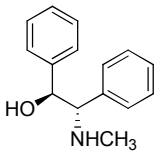
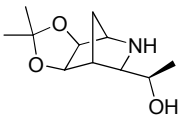
[19] Baratta, W.; Benedetti, F.; Del Zotto, A.; Fanfoni, L.; Felluga, F.; Magnolia, S.; Putignano, E.; Rigo, P. *Organometallics* **2010**, *29*, 3563.
[20] Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1996**, 233.
[21] Nordin, S. J. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431.
[22] a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562; b) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285.
[23] a) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318; b) Cheung, F. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. *J. Org. Chem*, **2005**, *70*, 3188; c) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc*. **2004**, *126*, 986.
[24] Gladiali, S; Taras, R. in *Modern Reduction Methods*; Andersson, P. G.; Munslow, I. J. Eds.; Wiley-VCH, Weinheim, **2008**, p. 135.

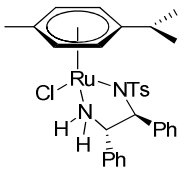


3



4

Amino alcohols and monotosylated diamine ligands are normally used together with Ru, Rh or Ir half-sandwich complexes to form bifunctional catalysts.[16a] Besides inducing enantioselectivity, the chiral ligand accepts and donates a proton with its basic nitrogen, whereas the hydride is received and delivered by the transition metal, as illustrated in Scheme 1.[25]



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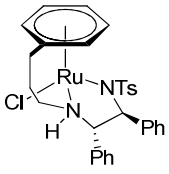
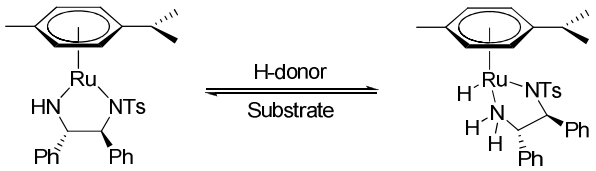


6

Complex **5** (Ru-TsDPEN, where DPEN = 1,2-diphenylethylenediamine), developed and thoroughly studied by Noyori, is perhaps the most well-known and successful catalyst for asymmetric transfer hydrogenation.[26] The tethered version of this catalyst, **6**, shows enhanced activity and selectivity in several cases over the untethered diamine due to the locked conformation of the arene.[23]



Scheme 1. Ru-TsDPEN as an example of bifunctional catalyst.

The class of substrates that can be highly selectively reduced by catalysts containing Ru, Rh or Ir half-sandwich complexes is limited to aryl alkyl ketones. The high selectivity associated with these reactions is ascribed to a stabilizing dipolar interaction between the arene-CH of the catalyst (e.g. *p*-cymene) and the π-system of the substrate.[27] When reducing dialkyl ketones

[25] a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931; b) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466.
[26] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.
[27] a) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2818; b) Alonzo, D. A.; Brandt, P.; Nordin S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580.

in hydrogen transfer reactions, the resulting enantioselectivities have so far been rather moderate. The only exceptions are the ruthenium catalysts based on either a β-cyclodextrin coupled amino alcohol ligand presented by Woggon and co-workers,[28] or ligand **1** developed by Reetz, which have shown promising selectivities for this transformation.[18,24] Nevertheless, the development of additional methods for the reduction of dialkyl ketones is highly desirable.

1.1.2 Hydrogen donors

The most widely used reaction media and hydrogen donors for transfer hydrogenation are 2-propanol, and the azeotrope of formic acid and triethylamine 5:2 (triethyl ammonium formate, TEAF, in formic acid). In recent years, it has become increasingly popular to perform asymmetric transfer hydrogenation reactions in water using alkali formate salts as the hydrogen source;[8,15] however, the selectivities have not until recently matched those obtained in the 2-propanol or TEAF systems.[29]

The 2-propanol conditions often include alkali isopropoxide as base and the donor is used in large excess to compensate for the unfavorable thermodynamics associated with this system. The equilibrium can also be shifted towards the product by distilling off acetone throughout the reaction. TEAF and alkali formate salts are more convenient hydrogen donors, since they irreversibly form carbon dioxide upon hydrogen donation. Despite this major advantage, only a limited number of catalysts are compatible with the formic acid conditions.[24] The strong interactions between the donor and the catalyst can result in inhibition or even decomposition of the catalyst.

A few years ago, Williams and co-workers published a new way of circumventing the unfavorable equilibrium, where 1,4-butanediol was used as the hydrogen donor, which irreversibly forms γ-butyrolactone upon two consecutive hydrogen transfers.[30] Other alcoholic media that have recently been explored for transfer hydrogenation reactions are ethanol[22b,31] and glycerol.[32]

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[28] a) Schlatter, A.; Woggon, W. D. *Adv. Synth. Catal.* **2008**, *350*, 995; b) Schlatter, A.; Kundu, M. K.; Woggon, W. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 6731.

[29] a) Matharu, D. S.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Chem. Commun.* **2006**, 3232; b) Wang, F.; Liu, H.; Cun, L.; Zhu, J.; Deng, J.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 9424; c) Wu, X.; Vinci, D.; Ikariya, T.; Xiao, J. *Chem. Commun.* **2005**, 4447; d) Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* **2004**, *2*, 1818.

[30] a) Maytum, H. C.; Francos, J.; Whatrup, D. J.; Williams, J. M. J. *Chem. Asian. J.* **2010**, *5*, 538; b) Maytum, H. C.; Tavassoli, B.; Williams, J. M. J. *Org. Lett*. **2007**, *9*, 4387.

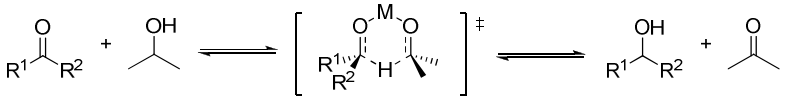
[31] a) Zweifel, T.; Scheschkewitz, D.; Ott, T.; Vogt, M.; Gruetzmacher, H. *Eur. J. Inorg. Chem.* **2009**, 5561; b) Zweifel, T.; Naubron, J-V.; Buttner, T.; Ott, T.; Gruetzmacher, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3245; c) Lundberg, H.; Adolfsson, H. *Tetrahedron Lett.* **2011**, in press.

[32] Wolfson, A.; Dlugy, C.; Shotland, Y.; Tavor, D. *Tetrahedron Lett.* **2009**, *50*, 5951.

When performing the ATH-reaction in water, the use of aqueous micellar catalysis often accelerates the reaction and can moreover give rise to an increase in selectivity.[33] Another approach is to adjust the catalyst system to aqueous conditions by increasing the hydrophilicity of the catalyst. Water-soluble monosulfonylated diamine ligands have been synthesized and evaluated in the aqueous ATH-reaction, where additional sulfonation on the arene of the TsDPEN ligand is one example.[34,35] A catalyst that works efficiently in alcoholic media is often not compatible with the formic acid or water conditions and *vice versa*. Noyori's catalyst Ru-TsDPEN, **5** is an exception, since it is rather efficient and highly selective in all the reaction media mentioned.[15,26]

1.1.3 Mechanistic overview

Transfer hydrogenation reactions can proceed via two fundamentally different mechanisms. Hydrogen transfer can occur directly from donor to substrate, or hydrogen can be delivered in a stepwise manner by first forming a metal hydride intermediate, which consecutively reduces the substrate.[25] Main group metals mediate direct hydrogen transfer, whereas transition metal complexes preferentially react via the hydride route.[26] The direct hydrogen transfer is believed to proceed via a six-membered cyclic transition state where both the substrate and the donor are simultaneously coordinated to the metal.[36] The MPV-reaction is an example where this mechanism is operating, as illustrated in Scheme 2. The metal acts as a Lewis acid, and activates the substrate towards hydride attack from the hydrogen donor.



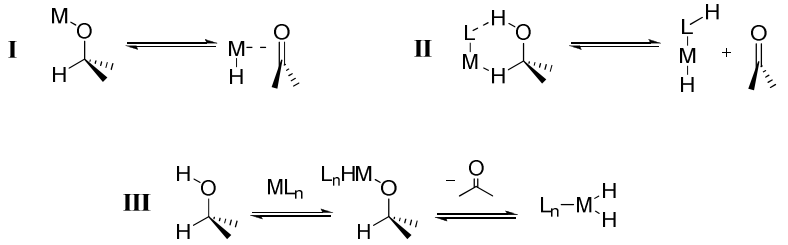
Scheme 2. Direct hydride transfer. M = metal.

In the case of metal hydride formation, the active catalyst is either a monohydride complex or a dihydride complex, depending on the nature of the

[33] Lindström, U. M. *Chem. Rev*. **2002**, *102*, 2751.
[34] a) Thorpe, T.; Blacker, J.; Brown, S. M.; Bubert, C.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4041; b) Bubert, C.; Blacker, J.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Thorpe, T.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4037.
[35] a) Barrón-Jaime, A.; Narvaez-Garayzar, O. F.; Gonzáles, J.; Ibarra-Galván, V.; Aguirre, G.; Parra-Hake, M.; Chávez, D.; Somanathan, R. *Chirality* **2011**, *23*, 178; b) Zhou, Z.; Ma, Q.; Sun, Y.; Zhang, A.; Li, L. *Heteroat. Chem.* **2010**, *21*, 505; c) Zhou, Z.; Sun, Y. *Catal. Commun.* **2009**, *10*, 1685; d) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett*. **2003**, *5*, 2103.
[36] Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.

metal catalyst. In the monohydride route, the hydride and proton maintain their identity throughout the reaction, whereas the hydrides in a dihydride mechanism lose their identity. The monohydride route can be further divided into an inner- and an outer-sphere mechanism. The inner-sphere mechanism involves a metal alkoxide intermediate, which after β-elimination of hydrogen generates the metal hydride (Scheme 3, **I**).[7] In the outer-sphere mechanism, the donor and substrate do not coordinate to the metal at any point. Hydrogen is instead transferred in a concerted or step-wise manner via a six-membered transition state (Scheme 3, **II**).[7] Metal hydride intermediates formed in this fashion have been isolated and reported by Noyori and coworkers.[22] A special case of the outer-sphere mechanism has recently been suggested and involves the simultaneous transfer of a hydride and an alkali cation instead of a proton.[37] The alkali cation acts as a Lewis acid and activates the ketone in a MPV-like fashion.

The formation of a metal dihydride is illustrated in Scheme 3 (**III**), where the two hydrides become equivalent when bound to the metal.[38] An early example of a catalyst system that follows the dihydride route is a ruthenium complex containing phosphine ligands.[13]

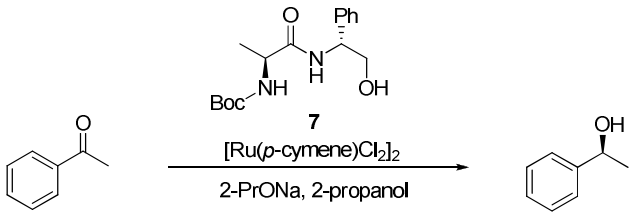


Scheme 3. Formation of metal monohydrides **I** and **II**, and metal dihydride **III**. L = ligand.

[37] a) Wettergren, J.; Buitrago, E.; Ryberg, P.; Adolfsson, H. *Chem. Eur. J.* **2009**, *15*, 5709; b) Västilä, P.; Zaitsev, A. B.; Wettergren, J.; Privalov, T.; Adolfsson, H. *Chem. Eur. J.* **2006**, *12*, 3218.
[38] Laxmi, S. Y. R.; Bäckvall, J-E. *Chem. Commun.* **2000**, 611.

2. Ligand design and catalyst development for ATH in 2-propanol

In the development of new ligands for asymmetric metal catalysis, it is desirable to utilize inexpensive and easily accessible chiral building blocks in their synthesis. Short peptides can favorably be chosen for this purpose due to the highly modular structure of these compounds. Derived from *N*-Boc-protected amino acids and amino alcohols, pseudo-dipeptides were previously developed and successfully used as ligands in the Ru-catalyzed ATH-reaction.[39] [Ru(*p*-cymene)Cl_2]$_2$ is used as the catalyst precursor in the reduction, which allows for the *in situ* formation of the active catalyst. The conversion of aryl alkyl ketones into the corresponding chiral secondary alcohols is fast and highly enantioselective employing these catalysts. It was found that the configuration of the amino acid part of the ligand strongly influences the absolute stereochemistry of the product, regardless of the configuration of the amino alcohol part. Thus, using a pseudo-dipeptide derived from the natural amino acid with *S*-configuration, such as **7** in Scheme 4, the *S*-isomer of the product is obtained.

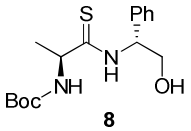


Scheme 4. ATH of acetophenone employing the pseudo-dipeptide ligand **7**.

The stability of the ruthenium complex with ligand **7** is poor, which is supported by the fact that the catalyst lifetime is short and no active catalyst intermediate has been isolated nor detected by any spectroscopic method so far. A probable explanation is the weak coordination between the ligand and the metal. By increasing the acidity of the central amide proton in the ligand, a tighter and thus, more robust complex could possibly form. The increased

[39] a) Västilä, P.; Wettergren, J.; Adolfsson, H. *Chem. Commun*. **2005**, 4039; b) Bøgevig, A.; Pastor, I. M.; Adolfsson, H. *Chem. Eur. J.* **2004**, *10*, 294; c) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Eur. J.* **2003**, *9*, 4031.

stability should result in prolonged catalyst lifetime, and improved selectivity could perhaps also be achieved. The central amide functionality was hence converted into the corresponding thioamide, since the pK_a-value for this functional group is considerably lower than for the corresponding carboxamide (around 18 versus 25 in DMSO).[40]



8

The thioamide ligand **8** in combination with [Ru(*p*-cymene)Cl_2]$_2$ was indeed found to catalyze the ATH-reaction. Surprisingly, however, the resulting alcohol had opposite configuration as compared to when the pseudo-dipeptide system was used.[41] After optimization, it was found that the selectivity was further increased when [RhCp*Cl_2]$_2$[42] was used as metal source. In contrast to the pseudo-dipeptide, where the OH-group in the amino alcohol part is crucial for efficient catalysis, superior results were obtained when excluding this functionality from the thioamide structure. The binding ability is thereby reduced from possible tridentate (coordination with the carbamate functionality, the carboxamide/thioamide and the hydroxyl group) to bidentate.

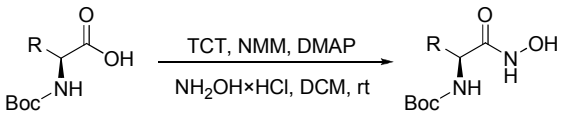
In order to find out whether the observed enantioswitch was a result of the increased acidity of the ligand, a new amino acid-derived ligand structure was designed, namely the hydroxamic acid, where increased acidity of the amide functionality was introduced in a different manner (pK_a around 16 in DMSO).[40] In addition, amino acid hydrazides (pK_a around 22 in DMSO)[40] were prepared and evaluated as ligands in the ATH-reaction as described in publication III; however, inferior catalyst performance was observed as compared to using the hydroxamic acids.

2.1 Hydroxamic acids (publication I)

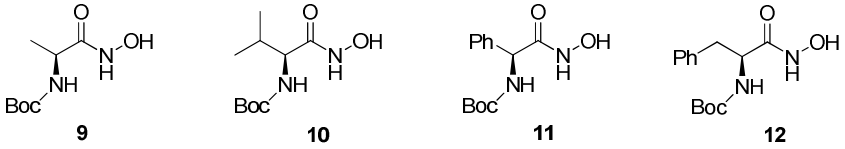
It is desirable to use simple and low-molecular weight ligands in transition metal catalysis. Amino acid-derived hydroxamic acids are nice examples thereof, where only inexpensive starting materials are used in their preparation. Various natural amino acids were used in the synthesis of hydroxamic

[40] pK_a values from: http://www.chem.wisc.edu/areas/reich/pkatable, 2011.
[41] Zaitsev A. B.; Adolfsson H. *Org. Lett.* **2006**, *8*, 5129.
[42] Cp* = pentamethyl cyclopentadienyl

acid ligands **9-12** following a one-pot procedure reported by Giacomelli and co-workers,[43,44] as shown in Scheme 5.



Scheme 5. Preparation of hydroxamic acid ligands. TCT = cyanuric chloride and NMM = *N*-methylmorpholine.



Ligands **9-12** were evaluated in the Rh-catalyzed[45] ATH of acetophenone in 2-propanol and the results are presented in Table 1. *S*-configured products were observed using catalysts derived from these ligands, which again is an enantioswitch as compared to the use of thioamide complexes. It suggests that instead of the increased ligand acidity, other properties of the catalyst govern the selectivity of the process. An obvious possibility is a difference in coordination mode of the two ligands, as an explanation for the switch.

Catalysts based on ligands **9**, **10** and **12** all showed promising activity and enantioselectivity, where the highest enantiomeric excess (ee) was achieved using ligand **10** (entry 5, Table 1). Superior activity was in fact obtained with ligand **11** (entry 6, Table 1); however, the selectivity was negligible in this case. Using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst precursor together with hydroxamic acid ligands, resulted in significantly lower activity (entry 3, Table 1), whereas the selectivity was less affected.

The effect of Lewis acidic additives was previously studied in the pseudo-dipeptide system, where it was found that the addition of a lithium salt had a positive impact on both selectivity and activity in the ATH-reaction.[37] The same trend was observed when using the thioamides, and accordingly, the addition of LiCl (5 mol%) to the hydroxamic acid system did indeed improve the catalyst performance, where enhanced enantioselectivities were obtained.

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[43] Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett*. **2003**, 5, 2715.
[44] Since the yields reported in the previous reference were difficult to reproduce, a different procedure was also used for the preparation of hydroxamic acids: Massaro, A.; Mordini, A.; Reginato, G.; Russo, F.; Taddei, M. *Synthesis* **2007**, 3201.
[45] $[RhCp^*Cl_2]_2$ was used as the catalyst precursor.

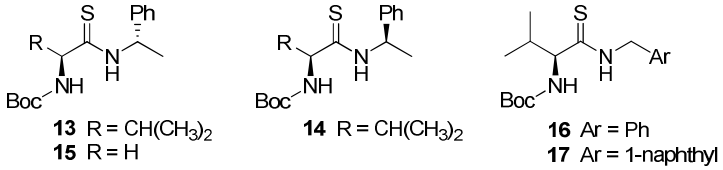
Table 1. Hydroxamic acid ligands **9**-**12** in the Rh-catalyzed ATH of acetophenone.[a]

Entry	Ligand	t [min]	Conversion [%][b]	ee [%][b]
1	**9**	30	66	82 (*S*)
2[c]	**9**	30	56	88 (*S*)
3[d]	**9**	30	4	71 (*S*)
4	**10**	120	89	87 (*S*)
5[c]	**10**	120	82	97 (*S*)
6	**11**	120	95	12 (*S*)
7	**12**	120	45	86 (*S*)
8[c]	**12**	120	63	92 (*S*)

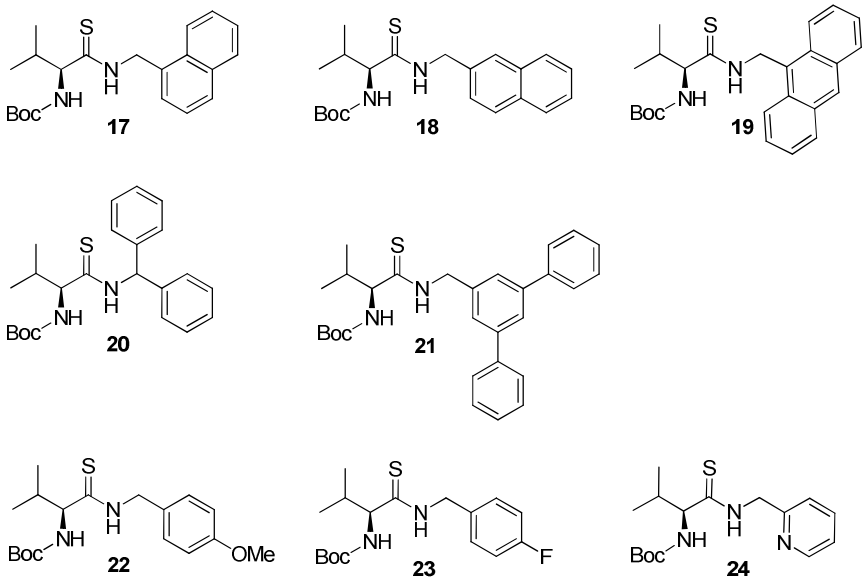
[a] Reduction of 1 mmol acetophenone using $[RhCp^*Cl_2]_2$ (S/C 200/1) and 0.5 mL 2-PrONa (0.1 M, 5 mol%) in 4.5 mL 2-propanol at rt. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB). [c] 5 mol% LiCl was added to the reaction mixture. [d] $[Ru(p\text{-cymene})Cl_2]_2$ was used as the catalyst precursor.

2.2 Thioamides (publication II)

In the original study using thioamide ligands together with $[RhCp^*Cl_2]_2$ for the ATH-reaction, it was found that the valine-derived ligand **13** gave the highest selectivity.[41] Moreover, the stereochemical outcome of the reaction was primarily correlated with the configuration of the amino acid part of the ligand, which is stressed by the fact that using the diastereomeric ligand **14** resulted in about equal degree of selectivity. In addition, when employing the corresponding glycine-derived ligand **15**, the activity is considerably reduced and the selectivity is almost completely lost (see chapter 3.1). The stereogenic center at the C-terminus on the other hand can be excluded without a significant loss in activity or selectivity, as in structure **16** (see chapter 3.1). Employing a ligand containing a larger substituent at this position, such as structure **17**, the selectivity is in the same range as using a catalyst based on the structurally more complex ligand **13** (*vide infra*). It is thus possible to use a structurally simpler thioamide-based catalyst in the ATH-reaction, i.e. containing a ligand with only one stereogenic center, and achieve equal catalyst performance as when employing the ligand having two sterogenic centers. In order to find out whether the substituent at the C-terminus had additional impact on the catalyst performance, further investigations were executed.



The thioamide ligands **17**-**24** were prepared from the corresponding amides using Lawesson's reagent.[41] A number of ligands containing substituents of varying size and with different electronic properties at the C-terminus were evaluated in the Rh-catalyzed ATH-reaction of acetophenone in 2-propanol. The results from the ligand screen are presented in Table 2.



Good activity and excellent selectivity was observed for catalysts based on all of the ligands, as can be seen in Table 2. Ligand **18** gave the most promising results with an ee of 96% (*R*) of 1-phenylethanol (entry 2, Table 2). Obviously, the introduction of larger aryl substituents in the C-terminus has a favorable impact on the selectivity but only to a certain extent. When employing the sterically demanding ligand **19**, derived from 9-(aminomethyl)-anthracene, the selectivity was somewhat reduced (entry 3, Table 2), whereas using the even bulkier ligand **21**, the activity was substantially lower, even if the selectivity was more or less retained (entry 5, Table 2). None of the ligands **22**-**24**, possessing different electronic properties, did have any positive influence on the catalyst performance (entries 6-8, Table 2).

Table 2. Thioamide ligands **17-24** in the Rh-catalyzed ATH of acetophenone.[a]

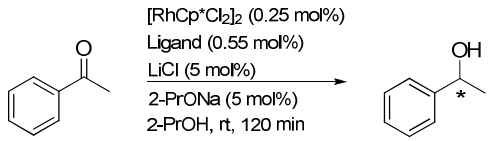
Entry	Ligand	t [min]	Conversion [%][b]	ee [%][b]
1	**17**	30	85	93 (*R*)
2	**18**	30	81	96 (*R*)
3	**19**	120	88	89 (*R*)
4	**20**	30	84	91 (*R*)
5	**21**	120	47	92 (*R*)
6	**22**	30	71	94 (*R*)
7	**23**	30	80	94 (*R*)
8	**24**	120	63	92 (*R*)

[a] Reduction of 1 mmol acetophenone using $[RhCp^*Cl_2]_2$ (S/C 200/1), 5 mol% LiCl and 0.5 mL 2-PrONa (0.1 M, 5 mol%) in 4.5 mL 2-propanol at rt. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB).

2.3 Evaluation of substrate scope

The optimizations described in chapters 2.1 and 2.2 revealed that 1-phenylethanol could be obtained in high levels of enantioselectivity of either configuration, depending on the choice of ligand used. The valine-derived hydroxamic acid ligand **10** showed the most promising results in the catalyst screen of this ligand class, and was further used to study the scope of the reaction (Table 3). For the thioamides, a number of ligands performed more or less equally well in the reduction of acetophenone. A multidimensional screen with different substrates and ligands was thus performed, in order to find the optimal catalyst for each substrate (see publication II). With the information obtained from such a screen, it is possible to fine-tune the catalyst depending on the nature of the substrate. However, thioamide ligand **18** showed the overall best catalytic results in the ligand screen of thioamides, and was thus used in a more extensive substrate screen (Table 4).

The reaction conditions used in the two screens are presented in Scheme 6. Differently functionalized acetophenones were evaluated, representing both electron poor and electron rich substrates. In addition, ketones having different degree of potential steric hindrance on the aryl ring or in the α-position were evaluated with the thioamide-based catalyst. Furthermore, ATH of some aliphatic ketones was attempted.

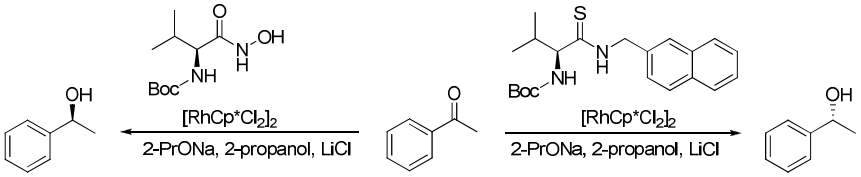


Scheme 6. Reaction conditions employed in the substrate screens.

From the substrate screen it was observed that for either catalyst, the acetophenones substituted with electron withdrawing groups are readily reduced into the corresponding alcohols, whereas the electron rich substrates react slower and with slightly lower selectivity. Using the hydroxamic acid-based catalyst, the highest selectivity is obtained in the reduction of acetophenone (entry 1, Table 3), where the ee measured is 97% (*S*). Equally high selectivity but with opposite configuration was achieved with the thioamide-containing catalyst in the reduction of 1-propiophenone (entry 2, Table 4).

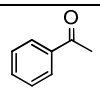
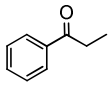
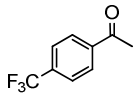
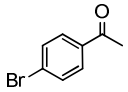
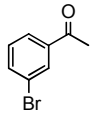
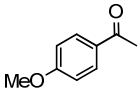
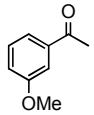
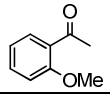
As previously observed for most ATH-protocols, the catalyst system based on thioamide ligands is evidently not appropriate for asymmetric reduction of dialkyl ketones; even if geranylacetone is readily reduced, this reaction takes place without any stereocontrol (entry 11, Table 4).

The two catalyst systems presented here proved to be highly efficient in the reduction of a number of aryl alkyl ketones. Besides the excellent selectivities associated with these ligand classes, the fact that chiral secondary alcohols of either configuration can be generated make them interesting and attractive to use in catalysis (Scheme 7). This feature can be most useful in a situation where only one enantiomer of the chiral starting material is available for the ligand synthesis. Furthermore, for amino acid-derived ligands, the natural amino acids are considerably less expensive than their enantiomers; consequently the choice of functionalization of the naturally occurring enantiomer for directing the stereochemical outcome of the reaction is of utmost interest.



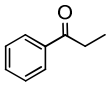
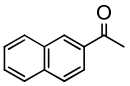
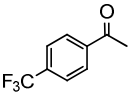
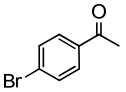
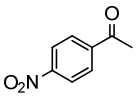
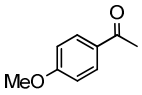
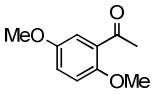
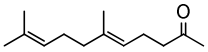
Scheme 7. Both product enantiomers can be obtained in the ATH of ketones depending on the choice of ligand functionalization.

Table 3. Substrate scope in the Rh-catalyzed ATH using hydroxamic acid ligand **10**.[a]

Entry	Substrate	Conversion [%][b]	ee [%][b]
1		82	97 (*S*)
2		84	87 (*S*)
3		99	95 (*S*)
4		93	92 (*S*)
5		98	96 (*S*)
6		77	94 (*S*)
7		54	81 (*S*)
8		90	86 (*S*)
9		85	90 (*S*)

[a] Reduction of 1 mmol substrate using $[RhCp^*Cl_2]_2$ and ligand **10** (S/C 200/1), 5 mol% LiCl and 0.5 mL 2-PrONa (0.1 M, 5 mol%) in 4.5 mL 2-propanol at rt for 2 h. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB).

Table 4. Substrate scope in the Rh-catalyzed ATH using thioamide ligand **18**.[a]

Entry	Substrate	Conversion [%][b]	ee [%][b]
1[c]		81	96 (*R*)
2		87	97 (*R*)
3[c]		91	94 (*R*)
4[c]		>99	89 (*R*)
5		73	59 (*R*)
6[c]		96	91 (*R*)
7[d,e]		88	78 (*R*)
8		6	n.d.
9[c]		49	90 (*R*)
10[f]		49	91 (*R*)
11		93	rac
12		8	n.d.

n.d.= not determined. rac = racemate. [a] Reduction of 1 mmol substrate using $[RhCp^*Cl_2]_2$ and ligand **18** (S/C 200/1), 5 mol% LiCl and 0.5 mL 2-PrONa (0.1 M, 5 mol%) in 4.5 mL 2-propanol at rt for 2 h. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB). [c] 30 min. [d] Reaction mixture contains 1 mL of THF. [e] 15 min. [f] Result obtained with ligand **20**.

3. Mechanistic investigation (publication III)

As described in chapter 2, products of opposite configuration can be obtained employing hydroxamic acids or thioamides as ligands in the ATH-reaction.[46] It was thus concluded that the observed enantioswitch is not correlated with the inherent ligand acidity. Instead, it was assumed that the different ligands coordinate to the metal in different manners. Other factors that can affect the reaction and cause a change in the product configuration have been reported, the use of additives being one example.[47]

An investigation of catalyst performance upon structural ligand modifications was desired and was performed by synthesizing differently functionalized ligands and evaluating them in catalysis. In order to gain further understanding about the hydroxamic acid and thioamide catalyst systems, kinetic experiments were moreover executed.

3.1 Ligand coordination

Initial experiments were performed to find possible non-linear selectivity effects[48] in the hydroxamic acid and thioamide catalyst systems. Such analyses can provide important information about the active catalyst, and indicate whether a monomeric or dimeric complex is operating in the reaction. The opposite enantiomers of ligands **10** and **13** (*ent*-**10** and *ent*-**13**, respectively) were prepared to adjust and vary the enantiopurities of the catalysts. The ees of the products were thereafter plotted versus the various ligand enantiopurities, from which a linear relationship was obtained for both ligands. The linearity indicates that the active catalysts most likely are monomeric complexes containing one ligand species and one metal center, since the ee of the ligand is proportionally correlated with the selectivity with which the resulting alcohol is obtained. Possible coordination modes of the ligand to $[RhCp^*Cl_2]_2$ could hence be suggested for the hydroxamic acid and

[46] Examples of unexpected inversions in asymmetric synthesis are reported in: Bartók, M. *Chem. Rev.* **2010**, *110*, 1663.
[47] a) Inagaki, T.; Ito, A.; Ito, J-I.; Nishiyama, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9384; b) Furegati, M.; Rippert, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 3947.
[48] a) Kagan, H. B. *Adv. Synth. Catal*. **2001**, *343*, 227; b) Alonso, D. A.; Nordin, S. J. M.; Roth, P.; Tarnai, T.; Andersson, P. G. *J. Org. Chem.* **2000**, *65*, 3116; c) Blackmond, D. G. *J. Am. Chem. Soc*. **1997**, *119*, 12934.

thioamide, respectively (modes **A-G**, Figure 2). Coordinations resulting in seven- or larger membered rings are excluded here, since these are considerably less stable than the five- or six-membered rings, and are not likely to form.[49]

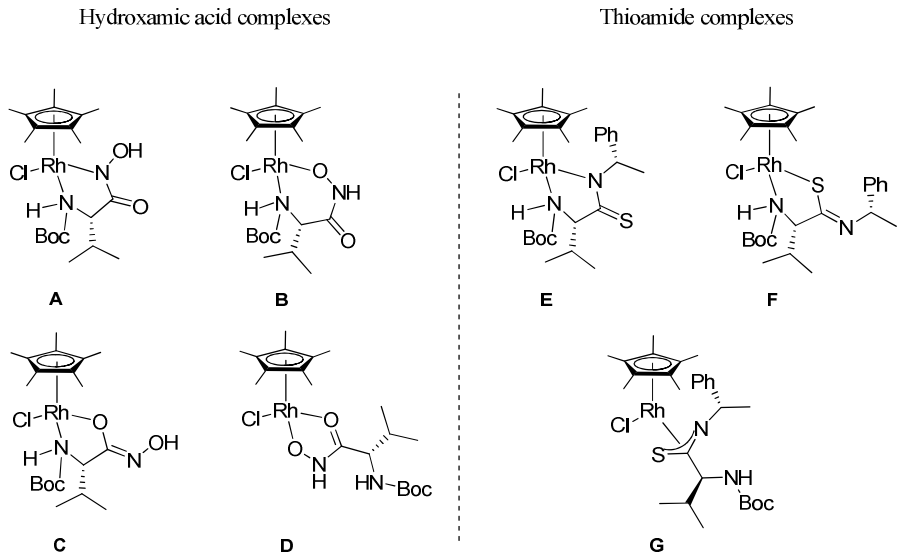
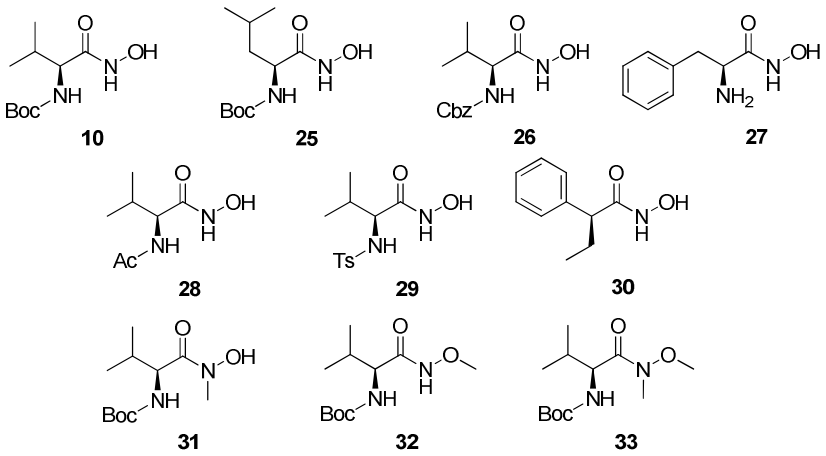


Figure 2. Potential coordination modes for the hydroxamic acid and thioamide to $[RhCp^*Cl_2]_2$, respectively.

In order to rule out some of the potential coordination modes, differently functionalized hydroxamic acids and thioamides were prepared and evaluated as ligands in the Rh-catalyzed ATH-reaction. The modified hydroxamic acids **25-33** were synthesized, and employed as ligands in the reduction of acetophenone, Table 5.

[49] Hancock, R. D. *J. Chem. Educ.* **1992**, *69*, 615.



10 **25** **26** **27**

28 **29** **30**

31 **32** **33**

Ligand **10** was discussed in chapter 2 and is used as a reference in the following investigation (entries 1 and 2, Table 5). Ligand **25**, derived from leucine, was prepared to elucidate whether the selectivity increases with increasing size of the amino acid side chain. However, the observed ee employing this ligand was similar to the enantioselectivity obtained with the valine-derived ligand (entries 3 and 4, Table 5).

To examine the importance of the protecting group, several modifications were made at the amino acid N-terminus. Replacing the Boc-group with the functionally similar Cbz-group (ligand **26**), resulted in comparable catalyst performance as with the reference ligand **10** (entries 5 and 6, Table 5). When the deprotected ligand **27** was employed, a decrease in both activity and selectivity was observed (entries 7 and 8, Table 5), and in addition, *R*-selectivity was obtained. Catalysts containing ligands **28** and **29** also gave poor results (entries 9-12, Table 5). Interestingly, however, *R*-configuration was obtained when reducing acetophenone with the rhodium complex of ligand **29** in the presence of LiCl (entry 12, Table 5). When substituting the amine with a tosyl group, the acidity of this functionality is considerably increased as compared to structure **10**. Therefore, the most basic site of the ligand, which in these catalysts presumably acts as the proton acceptor/donor, could change from the carbamate functionality to the hydroxamic acid functionality. The use of ligand **30**, lacking the N-terminus, resulted in complete loss of catalytic activity (entry 13, Table 5).

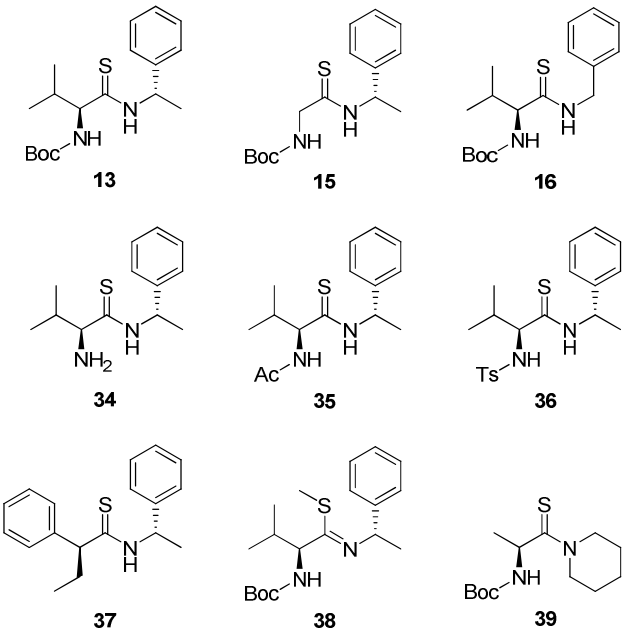
From the results obtained with ligands that are differently substituted at the C-terminus, it is possible to examine the importance of the hydroxamic acid functionality. The complex generated from the *N*-methyl hydroxamic acid ligand **31** almost completely lost its catalytic activity in the reaction, whereas slightly better results were obtained using the dimethyl ligand **33** (entries 14-15 and 18-19, respectively, Table 5). The observed activity when using the *O*-methyl hydroxamic acid ligand **32** was rather low, albeit the reaction proceeded with moderate selectivity (entries 16-17, Table 5).

Table 5. Evaluation of modified hydroxamic acids **25-33** in ATH of acetophenone.[a]

Entry	**Ligand**	**LiCl** [5 mol%]	**Conversion** [%][b]	**ee** [%][b]
1	**10**	-	89	87 (*S*)
2	**10**	+	82	97 (*S*)
3	**25**	-	43	89 (*S*)
4	**25**	+	62	95 (*S*)
5	**26**	-	76	90 (*S*)
6	**26**	+	80	92 (*S*)
7	**27**	-	13	21 (*R*)
8	**27**	+	64	34 (*R*)
9	**28**	-	1	-
10	**28**	+	2	-
11	**29**	-	2	-
12	**29**	+	8	53 (*R*)
13	**30**	-	4	-
14	**31**	-	-	-
15	**31**	+	2	-
16	**32**	-	16	70 (*S*)
17	**32**	+	10	36 (*S*)
18	**33**	-	8	5 (*S*)
19	**33**	+	11	18 (*S*)

[a] Reduction of 1 mmol acetophenone using $[RhCp^*Cl_2]_2$ (S/C 200/1) and 0.5 mL 2-PrONa (0.1 M, 5 mol%) in 4.5 mL 2-propanol at rt for 2 h. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB).

The modified thioamides **15-16** and **34-39** were synthesized, and employed as ligands in the reduction of acetophenone, Table 6.



Ligand **13** was previously found to be one of the best thioamide ligands, and is used as a reference structure in the following investigation (entries 1 and 2, Table 6).[41] From the results using ligands **15** and **16**, it can be concluded that the stereocenter in the amino acid part of the ligand is essential for inducing selectivity in the reaction, whereas the stereocenter in the amine part is of less importance (entries 3-6, Table 6). All modifications on the N-terminus lead to decreased catalyst performance. The deprotected ligand **34** gave rather poor selectivity even if the activity was maintained (entry 7, Table 6). When the N-terminus was substituted with an acetyl group (ligand **35**), the resulting activity and selectivity in the reduction was lower in comparison to the use of ligand **13** (entries 8 and 9, Table 6). The modified ligands **36-39** gave complete loss of activity when used in the Rh-catalyzed ATH-reaction of acetophenone (entries 10-14, Table 6). From these results it can be concluded that the nitrogen in the N-terminus is highly important and that a possibility for deprotonation of the amide functionality is necessary.

Table 6. Evaluation of modified thioamides **15**-**16** and **34**-**39** in ATH of acetophenone.[a]

Entry	**Ligand**	**LiCl** [5 mol%]	**Conversion** [%][b]	**ee** [%][b]
1	**13**	-	91	86 (*R*)
2	**13**	+	88	95 (*R*)
3	**15**	-	31	4 (*R*)
4	**15**	+	43	9 (*R*)
5	**16**	-	64	85 (*R*)
6	**16**	+	67	86 (*R*)
7	**34**	-	87	28 (*R*)
8	**35**	-	20	62 (*R*)
9	**35**	+	24	63 (*R*)
10	**36**	-	1	-
11	**36**	+	2	-
12	**37**	-	-	-
13	**38**	-	-	-
14	**39**	-	2	-

[a] Reduction of 1 mmol acetophenone using $[RhCp^*Cl_2]_2$ (S/C 200/1) and 0.5 mL 2-PrONa (0.1 M, 5 mol%) in 4.5 mL 2-propanol at rt for 2 h. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB).

From the presented results, it could be concluded that in order to achieve high catalyst activity and selectivity using the hydroxamic acid or thioamide ligands, the following criteria need to be fulfilled: 1) a substituent in the α-position is essential for the induction of enantioselectivity, 2) the N-terminus must be functionalized with a carbamate group, and 3) a possibility for deprotonation at the amide functionality is required. The N-terminus does most probably accept and donate the proton in both ligands, which means that the difference in coordination seems to arise from the acidic site of the ligand. The suggested modes of coordination for the hydroxamic acid **10** and thioamide **13** are thus **A** and **F**, respectively (Figure 2), where the deprotonated nitrogen is coordinating at the hydroxamic acid functionality and the sulfur atom is coordinating at the thioamide functionality.

In contrast to the previously described pseudo-dipeptide catalyst system, the increase in acidity for the thioamide ligand can in fact improve the catalyst stability, and as a result, a complex could be isolated and characterized by X-ray crystallography, Figure 3.

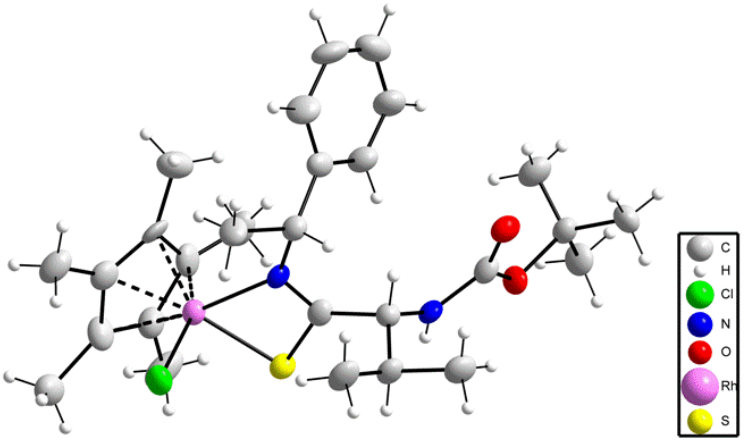


Figure 3. X-ray structure of the complex formed with ligand *ent*-**13** and $[RhCp^*Cl_2]_2$.

As revealed in the X-ray structure, the binding mode of ligand *ent*-**13** to $[RhCp^*Cl_2]_2$ is η^3-coordination of the thioamide functionality (structure **G**, Figure 2), and not the coordination mode suggested above (structure **F**, Figure 2). However, when employing this isolated complex in the reduction of acetophenone, moderate activity and extremely poor selectivity was achieved. It was therefore concluded that the isolated complex is a thermodynamically more stable rhodium complex, which is not equivalent to the catalytically active and selective complex formed *in situ*.

3.2 Initial rate kinetics

It is generally accepted that Ru, Rh and Ir half-sandwich complexes operate through the outer-sphere monohydride mechanism as described in chapter 1.1.3.[22b,25,27b] The transfer hydrogenation reaction catalyzed by these complexes can thus be divided into two consecutive steps, where the first step is metal hydride formation and the second step is the reduction of the substrate. However, it is desirable to gain additional mechanistic information about the catalytic systems containing hydroxamic acids and thioamides, and hence, kinetic experiments were consequently performed. By varying the concentration of one reaction component while keeping all other concentrations constant, it is possible to decipher how that specific component influences the overall rate of the reaction. The initial rate for each experiment is determined from the slope of the linear region when plotting the formation of product as a function of time. The reduction of acetophenone at varying hydrogen do-

nor concentrations is shown in Figure 4, where initial rates are plotted versus the various 2-propanol concentrations.[50]

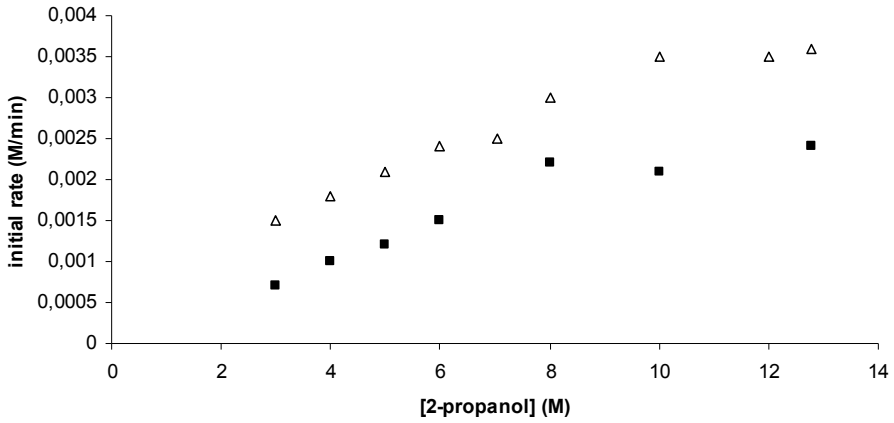


Figure 4. Initial reaction rates as a function of 2-propanol concentration (Rh-**10** ■, and Rh-**13** △).

The donor concentration is varied using THF as a co-solvent, since it does not interfere with the reaction. Apparently, a linear dependence on the 2-propanol concentration is found for the reaction catalyzed by both the hydroxamic acid and the thioamide complex. At very high donor concentrations, however (>8-10 M), saturation is achieved since the reaction rate is not further increased. It can thus be concluded that the reaction is pseudo-first order in donor concentration for both catalyst systems studied. The next reaction component to examine was the substrate, and initial rates were therefore measured at various ketone concentrations, as shown in Figure 5.

[50] Reaction conditions for all kinetic experiments are as presented in Scheme 6, chapter 2 (LiCl excluded). When adding co-solvents, the total volume was kept constant.

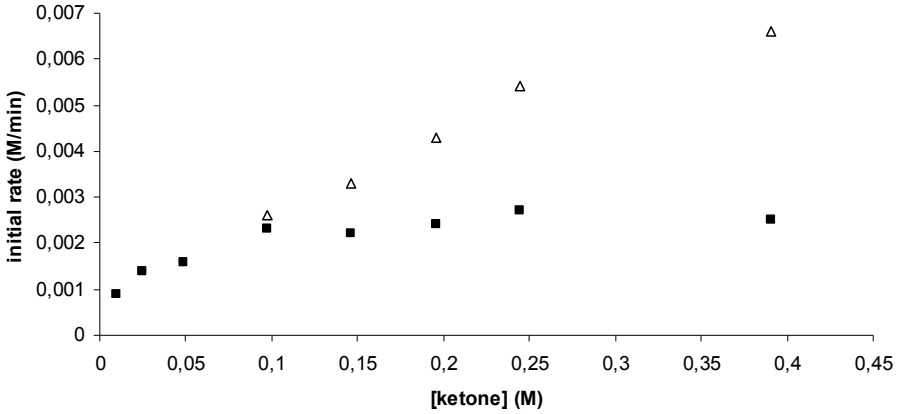


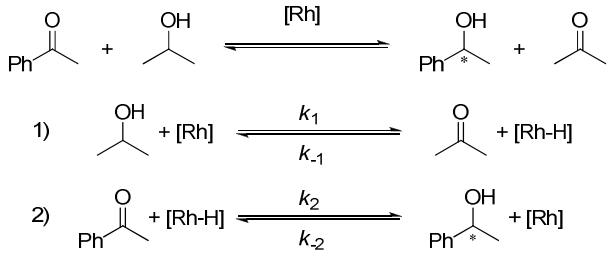
Figure 5. Initial reaction rates as a function of ketone concentration (Rh-**10** ■, and Rh-**13** △).

Different behaviors are in fact found for the two catalyst systems, where the thioamide-derived catalyst shows linear rate dependence on ketone concentration and the hydroxamic acid-derived catalyst shows rate independence. At high acetophenone concentration ([ketone] > 0.4 M), the substrate dependence was found to be of decreasing importance for the reaction catalyzed by the thioamide complex, which indicates pseudo-first order in substrate. The reaction catalyzed by the hydroxamic acid complex on the other hand shows a decrease in reaction rate when the acetophenone concentration is sufficiently low ([ketone] < 0.05 M), which indicates pseudo-zero order in substrate. At standard conditions, however, where the starting acetophenone concentration is around 0.2 M, the two catalyst systems have rather different rates and show diverse ketone dependences. The results imply that there is a difference in the rate determining step (RDS) in the reduction of acetophenone depending on which catalyst is used, where metal hydride formation is the RDS for the reaction catalyzed by the hydroxamic acid complex, and reduction of the substrate is rate limiting for the thioamide complex.

A Hammett plot was moreover derived, from which it was concluded that the reaction catalyzed by the thioamide complex is slightly more sensitive to substrate substitution than the corresponding hydroxamic acid complex, which is in line with the results obtained from the initial rate kinetic measurements (see publication III for further details).

3.3 Determination of rate constants

The reduction of acetophenone catalyzed by the rhodium complexes of hydroxamic acid or thioamide, respectively, can as aforementioned be divided into two consecutive steps, as illustrated in Scheme 8. Step one is the formation of a metal hydride, whereas step two is the reduction of the substrate. Both steps are reversible, and the corresponding rate constant for each transformation is defined as depicted in Scheme 8.



Scheme 8. Schematic representation of the individual reaction steps and the overall reduction process for the Rh-catalyzed ATH of acetophenone.

From the data obtained in the initial rate measurements, it is possible to determine the magnitude of the rate constants for the individual steps. The overall rate expression for the Rh-catalyzed ATH-reaction of acetophenone in 2-propanol is shown in Equation 1.[51]

$$\text{rate} = [\text{Rh}]_{\text{tot}} \left(\frac{k_1 k_2 [\text{2 - propanol}][\text{acetophenone}] - k_{-1} k_{-2} [\text{acetone}][\text{1 - phenylethanol}]}{k_1 [\text{2 - propanol}] + k_2 [\text{acetophenone}] + k_{-1} [\text{acetone}] + k_{-2} [\text{1 - phenylethanol}]} \right)$$

Eq. 1

The total rhodium concentration can be defined as in Equation 2, since it is not consumed during the course of the reaction.

$$[\text{Rh}]_{\text{tot}} = [\text{Rh}] + [\text{Rh - H}] \qquad \text{Eq. 2}$$

At an early stage of the reaction, the concentration of acetone and 1-phenylethanol is close to zero, and Equation 1 can thus be simplified to Equation 3.

[51] Wisman, R. V.; de Vries, J. G.; Deelman, B-J.; Heeres, H. J. *Org. Proc. Res. Dev.* **2006**, *10*, 423.

$$\frac{\text{rate}}{[\text{Rh}]_{\text{tot}}} = \frac{k_1 k_2 [2\text{-propanol}][\text{acetophenone}]}{k_1[2\text{-propanol}] + k_2[\text{acetophenone}]} \qquad \text{Eq. 3}$$

Inversion of Equation 3 generates Equation 4, which implies a linear relationship between the initial rate and the rate constants. Therefore, k_1 and k_2 can be determined by plotting the $[Rh]_{tot}$/initial rate ratio versus [acetophenone]$^{-1}$. Hence, k_1 can be obtained from the intercept ($1/k_1$[2-propanol]) and k_2 is given by the slope ($1/k_2$) of the straight line.

$$\frac{[\text{Rh}]_{\text{tot}}}{\text{rate}} = \frac{1}{k_1[2\text{-propanol}]} + \frac{1}{k_2[\text{acetophenone}]} \qquad \text{Eq. 4}$$

It is furthermore possible to determine k_{-1}, if initial rates are measured on reaction mixtures containing different acetone concentrations from the reaction start. The overall rate expression (Eq. 1) can thus be simplified to Equation 5.

$$\frac{\text{rate}}{[\text{Rh}]_{\text{tot}}} = \frac{k_1 k_2 [2\text{-propanol}][\text{acetophenone}]}{k_1[2\text{-propanol}] + k_2[\text{acetophenone}] + k_{-1}[\text{acetone}]} \qquad \text{Eq. 5}$$

Inversion of Equation 5 gives a linear correlation between the initial rate and the rate constant k_{-1} (Eq. 6). Accordingly, when plotting the $[Rh]_{tot}$/initial rate ratio versus [acetone], k_{-1} can be determined by using Equation 7, since the initial concentrations of 2-propanol and acetophenone, as well as k_1 and k_2 are known.

$$\frac{[\text{Rh}]_{\text{tot}}}{\text{rate}} = \frac{1}{k_1[2\text{-propanol}]} + \frac{1}{k_2[\text{acetophenone}]} + \frac{k_{-1}[\text{acetone}]}{k_1 k_2 [2\text{-propanol}][\text{acetophenone}]} \qquad \text{Eq. 6}$$

$$k_{-1} = \text{slope} \times k_1 k_2 [2\text{-propanol}][\text{acetophenone}] \qquad \text{Eq. 7}$$

k_{-2} can finally be obtained from k_1, k_2, k_{-1} and the equilibrium constant, according to Equation 8. The equilibrium constant was previously determined to be $K_{eq} = 0.13$ at 22 °C for the reduction of acetophenone in 2-propanol.[37a]

$$K_{\text{eq}} = \frac{k_1 k_2}{k_{-1} k_{-2}} = \frac{[\text{acetone}][1\text{-phenylethanol}]}{[2\text{-propanol}][\text{acetophenone}]} \qquad \text{Eq. 8}$$

The values of the individual rate constants obtained for the hydroxamic acid and thioamide catalyst system, respectively, are presented in Table 7.

Table 7. Initial rate constants for the Rh-catalyzed ATH-reaction of acetophenone.

	k_1 (M^{-1} min^{-1})	k_{-1} (M^{-1} min^{-1})	k_2 (M^{-1} min^{-1})	k_{-2} (M^{-1} min^{-1})
Hydroxamic acid **10**	0.198	69.4	137	3.01
Thioamide **13**	1.12	100	31.3	2.69

An alternative to the use of initial rate kinetics for the determination of rate constants is to make a simulated fit over the complete reaction profiles (until equilibrium is reached). The experimental data for the reactions catalyzed by the hydroxamic acid complex were modeled using the DynaFit software,[52] where a total of 257 data points were simultaneously fitted to give estimated values of k_1, k_{-1}, k_2 and k_{-2}. The values of the rate constants are in agreement with those obtained from the initial rate kinetics (see publication III for further details).

With the rate constants in hand, it is possible to determine the actual initial rates for the two steps by using Equations 9 and 10. The obtained rates for the two catalyst systems are presented in Table 8.

$$\text{rate step 1} = k_1[\text{Rh}]_{\text{tot}}[\text{2 - propanol}] \qquad \text{Eq. 9}$$

$$\text{rate step 2} = k_2[\text{Rh}]_{\text{tot}}[\text{acetophenone}] \qquad \text{Eq. 10}$$

Table 8. Initial rates for the Rh-catalyzed ATH-reaction of acetophenone.

	Initial rate step 1 (mM min^{-1})	**Initial rate step 2** (mM min^{-1})
Hydroxamic acid **10**	2.55	27.1
Thioamide **13**	14.5	6.18

As depicted in Equations 9 and 10, the rates are concentration dependent and will change during the course of the reaction concurrently with the turnover of acetophenone. With increasing accumulation of acetone and 1-phenylethanol, the reverse reactions will obviously become more prominent and have to be considered. Nevertheless, if k_2[acetophenone][Rh] >> k_1[2-propanol][Rh] at an early stage of the reaction, the metal hydride formation is rate determining (step 1). Conversely, if k_2[acetophenone][Rh] << k_1[2-propanol][Rh], step 2 becomes rate limiting. In the reaction catalyzed by the hydroxamic acid complex, the initial rate for step 1 is lower than the initial rate for step 2, as can be seen in Table 8, which suggests that hydride formation is the RDS. For the reaction catalyzed by the thioamide complex, the

[52] P. Kuzmic, *Anal. Biochem.* **1996**, *237*, 260.

opposite is observed, which implies that the reduction of acetophenone is the RDS.

3.4 Mechanistic conclusions

The results from the mechanistic investigation reveals a lot of information about the hydroxamic acid and thioamide catalyst systems. From the coordination study it could be concluded that the two ligands appear to bind the metal in a diverse fashion. The X-ray crystal structure of the thioamide complex shows a different coordination to the metal than first suggested (mode **G** versus **F**, Figure 2). However, besides the non-selective behavior of this complex when employed in catalysis, the reaction profile differs significantly from the reaction profile obtained under standard conditions (see publication III for further details), which indicates that the isolated complex is not equivalent to the *in situ* formed active catalyst operating in the reaction.

As a consequence of the difference in coordination mode between the ligands, a variation in the rate determining step is observed in the ATH-reaction of acetophenone catalyzed by these complexes, where the hydride formation is rate determining for the hydroxamic acid-derived complex and reduction of the substrate is rate limiting for the thioamide-derived complex. For comparison, in the ATH-reaction catalyzed by Noyori's Ru-TsDPEN complex, metal hydride formation is rate determining in 2-propanol, which is in accordance with the hydroxamic acid-based catalyst. In the formic acid/water system on the other hand, hydride formation becomes more facile and the RDS changes to ketone reduction.[25a,53]

By determining the rate constants for each reaction step of the overall reduction process, the actual initial rates could be determined for the forward reactions catalyzed by the hydroxamic acid and thioamide complex, respectively. A mechanistic summary is illustrated in Figure 6.

[53] a) Wu, X.; Liu, J.; Di Tommaso, D.; Iggo, J. A.; Catlow, C. R. A.; Basca, J.; Xiao, J. *Chem. Eur. J.* **2008**, *14*, 7699; b) Casey, C. P.; Johnson, J. B.; *J. Org. Chem.* **2003**, *68*, 1998.

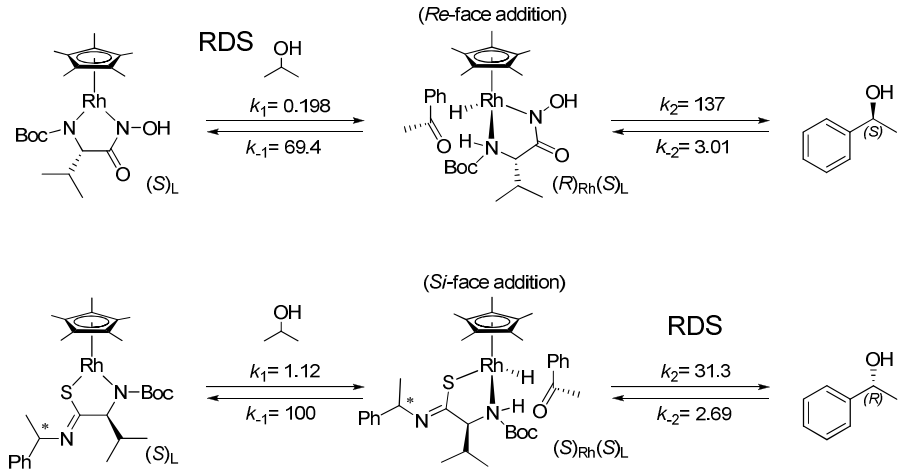


Figure 6. Summary of the mechanistic conclusions.

Before the metal receives a hydride it is diastereotopic, and the only stereocenter present in the complex is that of the ligand (which is of *S*-configuration in both the hydroxamic acid and the thioamide). Upon hydrogen transfer from 2-propanol to the complex, the rhodium ion becomes a stereogenic center and two possible diastereomeric complexes can in principle form. The high product selectivities of opposite configuration obtained with the two described catalysts indicate that different diastereomeric metal hydrides should form, which in turn react with the ketone to give the *S*- and *R*-isomer of the product, respectively. The $(S)_L(R)_{Rh}$-diastereomer should be energetically favored over the $(S)_L(S)_{Rh}$-diastereomer, since in the latter, the sterically demanding Boc-group would be in a disfavored eclipsed conformation with the amino acid side chain.[54] A potential explanation for the difference in configuration around the metal center is the divergence in electronic and steric properties of the two ligands, resulting from their different binding modes. The hydroxamic acid-containing rhodium complex can be stabilized by hyperconjugation from the lone pair on the hydroxyl oxygen into the σ*-orbital of the Rh-N bond. This stabilizing interaction lowers the energy of the complex; however, it also increases the electron density on the metal. As a result, the activation barrier for metal hydride formation should be elevated using this complex, because the rhodium ion is not as electrophilic towards hydride attack as in the thioamide complex. Since metal hydride formation is the RDS for the reaction catalyzed by the hydroxamic acid complex, the more stable hydride diastereomer $(S)_L(R)_{Rh}$ will preferentially form (see Figure 6). The *S*-isomer of 1-phenylethanol is subsequently ob-

[54] The disfavored steric interaction can be visualized in a Newman-projection through the carbamate nitrogen - α-carbon bond.

tained by hydride transfer from this complex to the *Re*-face of acetophenone. It is not expected that the hydride is delivered to the opposite side of the ketone, since in that case it would have to react without the important stabilizing interaction between the π-system of the substrate aryl ring and the arene-CH of the catalyst, as previously discussed in chapter 1.1.1.[27]

For the thioamide-containing complex, the metal hydride formation has a lower activation energy barrier relative to the ketone reduction step, which means that both metal hydrides can form and interconvert in a pre-equilibrium even if the $(S)_L(S)_{Rh}$ hydride is higher in energy. The path having the lowest activation barrier relative to the metal hydride intermediate will eventually lead to product formation, which for the thioamide catalyst presumably is via the energetically disfavored $(S)_L(S)_{Rh}$ hydride. This scenario can be explained by the Curtin-Hammett principle.[55] The dipolar stabilizing interaction between the substrate and the catalyst is of immense importance in the ketone reduction step, and thus the $(S)_L(S)_{Rh}$ hydride of the thioamide complex will react with the *Si*-face of acetophenone, leading to the *R*-alcohol as the major product.

The conclusions presented above are based on the experimental data obtained in the mechanistic investigation. However, it should be emphasized that the conclusions are in agreement with these results only if the correct mechanistic model is proposed, i.e. the outer-sphere monohydride mechanism. Furthermore, a positive effect on the catalyst activity and selectivity is observed for the hydroxamic acid and thioamide catalyst systems upon addition of lithium chloride to the reaction mixture (see chapter 2). The reason behind this effect has not been completely elucidated. In other similar catalyst systems, it has been shown that the solvent can be involved in the proton transfer,[56] which means that the mechanism for the ATH-reaction could be considerably more complex than anticipated here, and could perhaps be more correctly explained by other models and with other methods. DFT-calculations on the hydroxamic acid and thioamide catalyst systems are currently being pursued.

[55] Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, University Science Books, Sausalito, California, **2006**, p. 378.
[56] Handgraaf, J-W.; Meijer, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 3099.

4. Ligand design and catalyst development for ATH in water

The use of water as reaction medium has become increasingly popular for the ATH-reaction.[8,15] Applying the principles of green chemistry[57] is important and the avoidance of organic solvents is indeed a step in the right direction.[58] The typical hydrophobic nature of organic reactants can cause solubility problems for chemical transformations performed in aqueous media. However, it is possible to take advantage of the hydrophobic properties of the reaction components, since they can form droplets in the water medium, resulting in high local concentrations. The Diels-Alder reaction performed in water is an excellent example of this scenario, where improved reaction rates can be observed as compared to using organic solvents.[59]

One way of circumventing solubility problems in the aqueous ATH-reaction is to modify the reaction components into more hydrophilic species. As previously mentioned, functionalization of the TsDPEN ligand to create water soluble versions of the Noyori catalyst is a successful example of this strategy.[34,35] Furthermore, the use of phase-transfer components can facilitate the dissolution of reactants having diverse solubility properties. Micelles that form upon addition of surfactants to the reaction mixture can act as potential reaction cavities and can even enhance the activity and selectivity.[33]

Formate salts are suitable reducing agents for transfer hydrogenation in aqueous media, since they are readily available, and allow for reduction under mild conditions. Especially attractive is the irreversible nature of the hydrogen transfer using these salts, and as a consequence, improved reaction performance can be achieved as compared to the 2-propanol system. Nevertheless, the number of efficient catalysts that can operate under aqueous conditions is rather limited, and there is still room for further improvements.[24]

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[57] a) Gupta, M.; Paul, S.; Gupta, R. *Current Science* **2010**, 99, 1341; b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory & Practice*, Oxford University Press, New York, **1998**, 30.
[58] Wang, C.; Wu, X.; Xiao, J. *Chem. Asian. J.* **2008**, *3*, 1750.
[59] a) Tiwari, S.; Kumar, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4824; b) Sijbren, O.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, 72, 1365.

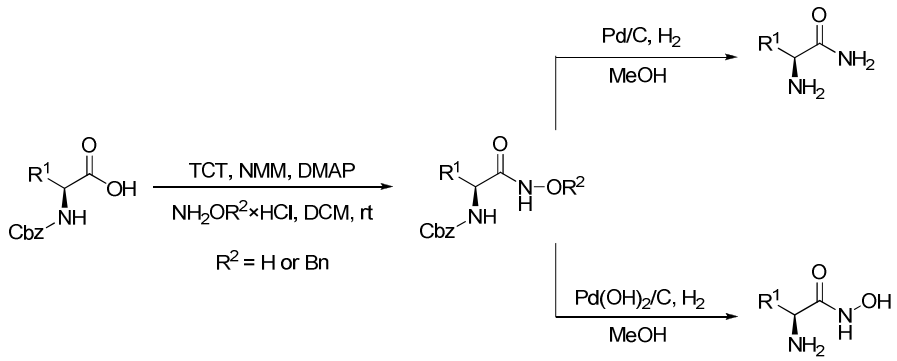
4.1 Amino acid amides and hydroxamic acids (publication IV)

Since it is desirable to develop catalysts for ATH that, in addition to the 2-propanol system, are competent under aqueous conditions, it was investigated whether the previously examined amino acid-derived hydroxamic acid ligands (see chapter 2.1) could prove useful for this task. The simple and versatile structure of these ligands makes them highly modular and attractive to use in catalysis. The fact that they generate low-molecular weight catalysts when coordinated to metals, and moreover, are prepared from inexpensive and easily accessible starting materials, proves the usefulness of such a ligand class, and makes it interesting to examine whether the field of applications can be further extended.

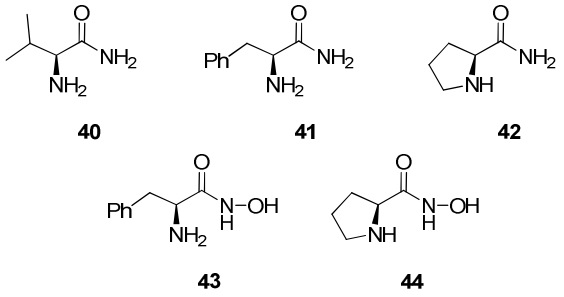
The structurally even simpler amino acid amides, which have previously been reported by Faller and Lavoie as ligands for the Ru-catalyzed ATH in 2-propanol, were also prepared and evaluated in the reaction performed in water.[60,61] Other amino acid-derived amide ligands have previously been developed and evaluated in aqueous ATH; however, they all contained different aryl-substituents at the C-terminus of the amino acid.[62]

The amides and hydroxamic acids **40-44** were prepared according to Scheme 9. Removal of the carbamate present in the original hydroxamic acid ligand structure turned out to be essential for the formation of an active catalyst that is operational in the aqueous system.[63] The two types of ligand structures could conveniently be obtained from the same protected hydroxamic acid intermediate, depending on which deprotection method was utilized.[64]

[60] Faller, J. W.; Lavoie, A. R. *Organometallics* **2001**, *20*, 5245.
[61] a) Bacchi, A.; Pelagatti, P.; Pelizzi, C.; Rogolino, D. *Organomet. Chem.* **2009**, *694*, 3200; b) Pelagatti, P.; Bacchi, A.; Calbiani, F.; Carcelli, M.; Elviri, L.; Pelizzi, C.; Rogolino, D. *J. Organomet. Chem.* **2005**, *690*, 4602; c) Pelagatti, P.; Carcelli, M.; Calbiani, F.; Cassi, C.; Elviri, L.; Pelizzi, C.; Rizzotti, U.; Rogolino, D. *Organometallics* **2005**, *24*, 5836.
[62] a) Mao, J.; Guo, J. *Chirality* **2010**, *22*, 173; b) Zhou, Z.; Wu, L. *Catal. Commun.* **2008**, *9*, 2539; c) Zeror, S.; Collin, J.; Fiaud, J-C.; Zouioueche, L. A. *J. Mol. Catal. A: Chem.* **2006**, *256,* 85; d) Rhyoo, H. Y.; Park, H-J.; Won, H. S; Chung, Y. K. *Tetrahedron Lett*. **2002**, 43, 269; e) Rhyoo, H. Y.; Park, H-J.; Chung, Y. K. *Chem. Commun.* **2001**, 2064; f) Rhyoo, H. Y.; Yoon, Y-A.; Park, H-J.; Chung, Y. K. *Tetrahedron Lett.* **2001**, *42*, 5045.
[63] Only 2% conversion was measured when employing the Boc-protected hydroxamic acid ligand **10** under otherwise identical reaction conditions.
[64] Rowley, M.; Leeson, P. D.; Williams, B. J.; Moore, K. W.; Baker, R. *Tetrahedron* **2002**, *48*, 3557.

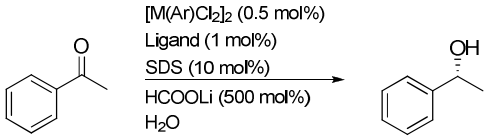


Scheme 9. Preparation of amino acid amides and hydroxamic acids via the same *N*-Cbz-protected hydroxamic acid intermediate.



40 **41** **42** **43** **44**

Ligands **40**-**44** were evaluated in the ATH-reaction of acetophenone according to the reaction conditions in Scheme 10, and the results are presented in Table 9. The surfactant sodium dodecyl sulfate (SDS) is used for the formation of micelles in water.



Scheme 10. Reaction conditions employed in the aqueous ATH-reaction. M = Rh/Ir/Ru. Ar = Cp*/*p*-cymene.

Excellent conversion and moderate selectivity was obtained using the L-valine-derived amide ligand **40** in combination with $[RhCp^*Cl_2]_2$; a somewhat higher ee was achieved when exchanging sodium formate for its lithium counterpart (entries 1 and 2, respectively, Table 9). The sterically more demanding L-phenylalanine-derived amide **41** did not improve the selectivity when used together with $[RhCp^*Cl_2]_2$; in fact lower ees were obtained employing this catalyst (entry 4, Table 9). Interestingly, however,

using $[IrCp^*Cl_2]_2$ as the catalyst precursor increased the selectivity of the reaction employing either of the amide ligands **40** and **41** (entries 3 and 5, respectively, Table 9).

A dramatic increase in selectivity along with substantially lower conversion was found using the more rigid amide ligand **42** together with $[RhCp^*Cl_2]_2$ (entry 6, Table 9). Presumably, the chelate ring formed upon coordination of the bidentate L-proline-derived amide to the metal is less flexible as compared to the other two amino acid-derived amides. With this ligand, the opposite trend is observed, and inferior selectivity was measured using $[IrCp^*Cl_2]_2$ as the catalyst precursor (entry 9, Table 9). The conversion on the other hand remains high in this case. Since it is desirable to use the most selective catalyst, it was investigated whether the performance using ligand **42** together with $[RhCp^*Cl_2]_2$ could be improved. When prolonging the reaction time, full conversion was obtained without any loss in selectivity (78% ee (*R*) after 70 h). To find the optimal balance between conversion, selectivity and time using the Rh-**42** complex, the reaction was carried out at various temperatures and it was concluded that 35°C is the temperature of choice employing this catalyst, since the ee remains rather high (entries 7 and 8, Table 9). At even higher temperatures (40°C), the decrease in selectivity was more severe (73% ee (*R*) after 18 h).

From the results obtained employing the hydroxamic acids, it is clear that the selectivity trend follows that of the amide ligands. Poor selectivity was achieved using the phenylalanine-derived ligand **43** (entry 10, Table 9) and higher ee was observed for the proline-derived ligand **44** (entry 11, Table 9). In contrast to the amide ligand derived from proline, ligand **44** in combination with $[RhCp^*Cl_2]_2$ can catalyze the reduction to completion at room temperature and shorter reaction time (*vide infra*). Superior selectivity was achieved in the reaction employing ligand **44** and $[IrCp^*Cl_2]_2$ (entry 13, Table 9), while the catalyst performance was surprisingly sluggish using $[Ru(p\text{-cymene})Cl_2]_2$ as the metal source (entry 14, Table 9).

When reflecting on the product configuration obtained employing hydroxamic acid ligands **10** and **44**, it evidently changes from the *S*-alcohol in the case of the Boc-protected ligand (see chapter 2.1) to the *R*-isomer when the deprotected hydroxamic acid ligand is used. One possible explanation could be that the RDS changes from being hydride formation in the 2-propanol system, to ketone reduction for the reaction carried out in water, which has been reported to be the case for the Noyori catalyst.[25a,53] Kinetic studies on the Rh-**44** catalyzed ATH-reaction in water should be executed in order to establish whether this suggestion is correct.

Table 9. Evaluation of ligands **40-44** in ATH of acetophenone.[a]

Entry	Metal	Ligand	Conversion [%][b]	ee [%][b]
1[c]	$[RhCp^*Cl_2]_2$	**40**	99	46 (*R*)
2	$[RhCp^*Cl_2]_2$	**40**	96	52 (*R*)
3[d]	$[IrCp^*Cl_2]_2$	**40**	99	71 (*R*)
4	$[RhCp^*Cl_2]_2$	**41**	99	34 (*R*)
5	$[IrCp^*Cl_2]_2$	**41**	99	43 (*R*)
6	$[RhCp^*Cl_2]_2$	**42**	55	78 (*R*)
7[e]	$[RhCp^*Cl_2]_2$	**42**	80	77 (*R*)
8[f]	$[RhCp^*Cl_2]_2$	**42**	99	76 (*R*)
9	$[IrCp^*Cl_2]_2$	**42**	99	72 (*R*)
10	$[RhCp^*Cl_2]_2$	**43**	99	29 (*R*)
11[d]	$[RhCp^*Cl_2]_2$	**44**	99	69 (*R*)
12[c,d]	$[RhCp^*Cl_2]_2$	**44**	99	68 (*R*)
13[d]	$[IrCp^*Cl_2]_2$	**44**	99	74 (*R*)
14[d,g]	$[Ru(p\text{-cymene})Cl_2]_2$	**44**	6	41 (*R*)

[a] Reduction of 1 mmol acetophenone (S/C 100/1) with 5 equiv. HCOOLi and 10 mol% SDS in 2.5 mL distilled H_2O at 28˚C for 17-22 h. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB). [c] HCOONa was used as the reducing agent. [d] 24˚C. [e] 32˚C. [f] 35˚C. [g] 40 h.

4.1.1 Evaluation of substrate scope

From the amino acid amide and hydroxamic acid ligand screen, it was found that the ligands derived from L-proline showed the most promising results. Ligand **42** and **44** were therefore used to study the scope of the reaction. Since the reduction catalyzed by the hydroxamic acid **44** in combination with $[IrCp^*Cl_2]_2$ gave slightly higher but still comparable selectivity as obtained with $[RhCp^*Cl_2]_2$, both catalyst precursors were evaluated in the substrate screen using this ligand. Differently functionalized and substituted acetophenones, representing both electron rich and electron poor substrates, were reduced employing catalysts based on the two ligands (Table 10 and Table 11, respectively). In addition, ketones having potentially larger steric hindrance either in the α-position or on the aryl ring were evaluated.

In the reactions catalyzed by the amide-containing complex, the obtained selectivities were overall good, whereas the conversions were good or even

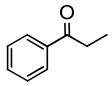
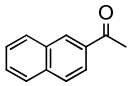
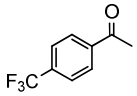
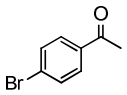
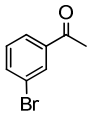
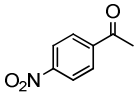
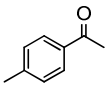
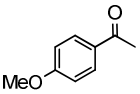
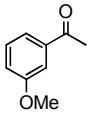
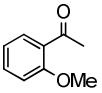
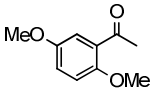
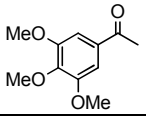
excellent for certain substrates (Table 10). The highest ees were measured for the reduction of 2-acetonaphtone (85%) and 3´-methoxyacetophenone (88%) into the corresponding *R*-configured secondary alcohols (entries 3 and 11, Table 10).

Excellent conversions were obtained for most substrates in the reactions catalyzed by the hydroxamic acid complexes, even at shorter reaction times and lower temperatures as compared to the reactions catalyzed by the amide complex (14 h at 24°C versus 18 h at 35°C). The selectivities were generally higher using $[IrCp^*Cl_2]_2$ as the metal source. The catalysts based on hydroxamic acid ligand **44** appear to be rather sensitive to substitution at the *ortho*-position of the aryl ring of the substrates, since the ees are significantly lower regardless of which catalyst precursor is used (entries 9-10 and 15-16, Table 11). The best results were achieved in the reduction of 2-acetonaphtone using $[IrCp^*Cl_2]_2$ (entry 4, Table 11) and 4´-methylacetophenone using $[RhCp^*Cl_2]_2$ (entry 11, Table 11), where equally high degrees of selectivity were measured (90% in favor of the *R*-isomer).

From the presented results it is evident that amino acid-derived amides and hydroxamic acids are efficient ligands in the aqueous ATH-reaction of aryl alkyl ketones. The amino acid side chain obviously influences the degree of selectivity in the reduction, since a correlation is found between the two ligand classes. In addition, the selectivities are in agreement with those obtained when simple amino acids are used as ligands together with $[RhCp^*Cl_2]_2$, under otherwise identical reaction conditions.[65] In the reduction of acetophenone, L-proline gives the highest selectivity of 1-phenylethanol (76% ee), L-valine gives 50% ee, and L-phenylalanine gives only 33% ee, all in favor of the *R*-isomer. Employing these ligands, the conversion was poor (around 20%); however, the reactions were carried out at room temperature. The use of amino acids in a first ligand screen without performing any derivatization into more complex ligand structures can provide information about the resulting selectivities. Equal degree of selectivity can hence be expected for similar catalyst systems, which makes it a simple and convenient method for further ligand developments.

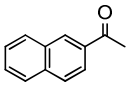
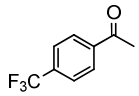
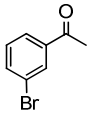
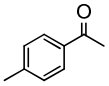
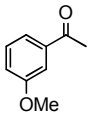
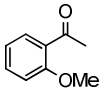
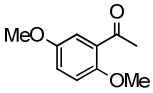
[65] An example where amino acids have been used directly as ligands is: Ohta, T.; Nakahara, S.-I.; Shigemura, Y.; Hattori, K.; Furukawa, I. *Chem. Lett.* **1998**, 491.

Table 10. Substrate scope in ATH using amide ligand **42**.[a]

Entry	Substrate	Conversion [%][b]	ee [%][b]
1		99	76 (*R*)
2		57	48 (*R*)
3		82	85 (*R*)
4		56	81 (*R*)
5		97	69 (*R*)
6		95	54 (*R*)
7		92	71 (*R*)
8		46	58 (*R*)
9		59	78 (*R*)
10		68	65 (*R*)
11		98	88 (*R*)
12		73	73 (*R*)
13		83	80 (*R*)
14		94	76 (*R*)

[a] Reduction of 1 mmol substrate using $[RhCp^*Cl_2]_2$ and ligand **42** (S/C 100/1) together with 5 equiv. HCOOLi and 10 mol% SDS in 2.5 mL distilled H_2O for 18 h at 35°C. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB).

Table 11. Substrate scope in ATH using hydroxamic acid ligand **44**.[a]

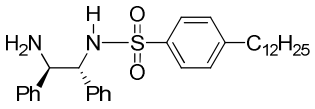
Entry	Substrate	Conversion [%][b]	ee [%][b]
1		98	70 (*R*)
2[c]		99	73 (*R*)
3		73	83 (*R*)
4[c]		99	90 (*R*)
5		96	69 (*R*)
6[c]		99	76 (*R*)
7		97	40 (*R*)
8[c]		97	52 (*R*)
9		95	31 (*R*)
10[c]		99	27 (*R*)
11		76	90 (*R*)
12[c]		86	80 (*R*)
13		95	62 (*R*)
14[c]		96	76 (*R*)
15		81	rac
16[c]		99	30 (*R*)
17		92	63 (*R*)
18[c]		98	76 (*R*)

[a] Reduction of 1 mmol substrate using $[RhCp^*Cl_2]_2$ and ligand **44** (S/C 100/1) together with 5 equiv. HCOOLi and 10 mol% SDS in 2.5 mL distilled H_2O for 14 h at 24°C. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB). [c] $[IrCp^*Cl_2]_2$ was used as the catalyst precursor.

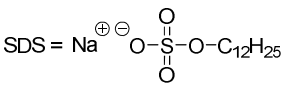
4.2 Modified sulfonylated diamine (publication V)

As discussed in chapter 1.1.1, there is no stabilizing dipolar interaction between the catalyst and substrate in the reduction of dialkyl ketones, which is essential for obtaining high selectivities in the ATH-reaction using half-sandwich catalysts. Aliphatic ketones thus have to be stabilized in alternative ways during the hydrogen transfer step in order to achieve equally high degrees of selectivity as obtained for aromatic ketones. One method that could allow for additional substrate stabilization is the use of aqueous micellar catalysts, along with an adjusted transition-metal catalyst that interacts properly with the micelles.

The Ru-TsDPEN complex is an excellent catalyst for transfer hydrogenation under aqueous conditions, and the TsDPEN ligand was hence modified to resemble the surfactant SDS, having one hydrophilic and one hydrophobic end (structure **45**).[66] The catalyst can thereby interact in an optimal way with the micelles, where the long alkyl chain interacts with the hydrophobic cavity, and the hydrophilic part (the metal site where the hydrogen transfer occurs) should be oriented towards the micelle surface, and thus the water phase.



45



Ketones with hydrophobic alkyl chains should act in the same manner, which in principle could result in a certain fixation of the catalyst and substrate orientations at the micelle surface. As a consequence, catalyst discrimination between the two enantiotopic faces of the prochiral ketone could possibly be achieved. The hypothesis is illustrated in Figure 7.

[66] Ligand **45** was prepared by converting the commercially available 4-dodecylbenzenesulfonic acid into the corresponding sulfonyl chloride using TCT and Et_3N in refluxing acetone, which was subsequently coupled with the commercially available 1,2-diphenylethylenediamine using Et_3N in DCM.

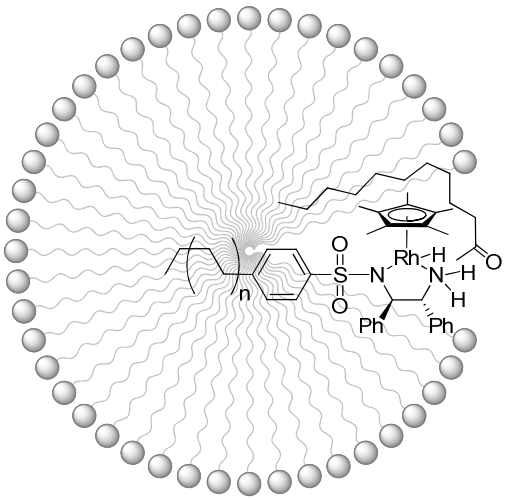


Figure 7. Hypothetic interaction between catalyst, substrate and micelle.

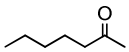
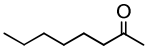
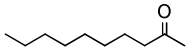
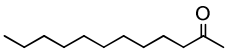
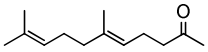
4.2.1 Evaluation of substrate scope

Employing the modified ligand **45** together with $[RhCp^*Cl_2]_2$ in the aqueous ATH-reaction resulted in higher selectivity as compared to using $[Ru(p\text{-cymene})Cl_2]_2$ (47% and 7% ee, respectively, in the reduction of 2-octanone). The former alternative was therefore chosen as the catalyst precursor. A substrate screen was performed for a range of aliphatic ketones having alkyl chains of varying lengths. In addition, ATH on geranyl acetone and cyclohexyl methyl ketone were evaluated. The reactions were carried out both in the presence and absence of surfactant, to find out whether a difference in activity and selectivity could be observed for the two cases. The results from the reductions are presented in Table 12. Excellent activity was noticed for most of the substrates, and a substantial positive effect on the conversion was observed upon addition of SDS to the reaction of 2-dodecanone (entries 7 and 8, Table 12). The reduction of 2-decanone gave similar results, albeit less pronounced in comparison to its slightly longer analogue (entries 5 and 6, Table 12). When reducing 2-heptanone and 2-octanone on the other hand, no significant improvement in conversion was obtained in the presence of SDS (entries 1-4, Table 12). It could thus be concluded that the addition of surfactants is more important when reducing substrates with longer alkyl chains, presumably due to their lower solubilities in water, as compared to shorter hydrocarbon chains. Cyclohexyl methyl ketone showed similar behaviour as the more hydrophobic ketones (entries 11 and 12, Table 12).

Regarding the selectivity, the effect of adding surfactants to the reaction mixture was rather insignificant, where slightly better selectivities were observed for certain substrates only. The measured ees were moderate in all

cases, except for the reduction of cyclohexyl methyl ketone, where quite good selectivity was measured (entries 11 and 12, Table 12). The enantioselectivity obtained for this particular substrate is in fact one of the highest reported under aqueous transfer hydrogenation conditions.[67] In order to find out whether the use of chiral surfactants in the ATH-reaction could result in additional enantiofacial differentiation, (-)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB) among other chiral surfactants, were evaluated in the ATH of aliphatic ketones. Unfortunately, no further improvement in the selectivity of the resulting secondary alcohols could be achieved.

Table 12. Substrate scope in ATH of dialkyl ketones using ligand **45**.[a]

Entry	Substrate	Conversion [%][b]	ee [%][b]
1		99	42
2[c]		98	42
3		97	39
4[c]		99	45
5		85	44
6[c]		96	47
7		46	43
8[c]		99	47
9		69	37
10[c]		74	38
11		83	84
12[c]		97	84

[a] Reduction of 1 mmol substrate using $[RhCp^*Cl_2]_2$ and ligand **45** (S/C 100/1) together with 5 equiv. HCOONa in 2.5 mL distilled H_2O for 17 h. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB). [c] 10 mol% SDS was added to the reaction mixture.

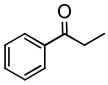
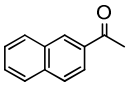
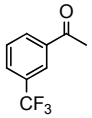
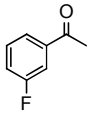
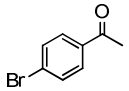
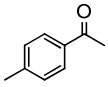
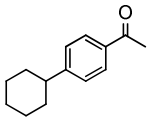
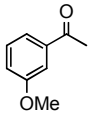
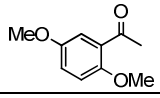
Even if moderate selectivities were generally obtained in the reduction of aliphatic ketones, the smooth reaction and relatively high activity of this particular catalyst system was encouraging. The catalyst was therefore evaluated under the same reaction conditions for the reduction of aryl alkyl ketones. It was indeed found that the catalyst was useful for this category of substrates, and the reduction of a number of differently substituted acetophenones proceeded in an efficient and highly enantioselective manner, as presented in Table 13. The conversions and ees obtained were excellent in all cases except for the reduction of 2´,5´-dimethoxyacetophenone (entry 10,

[67] Equally high level of selectivity was obtained in the following publication: Matharu, D. S.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Chem. Commun.* **2006**, 3232.

Table 13) and 2-acetonaphtone (entry 3, Table 13), where the results were somewhat poorer.

In order to find out whether the catalyst interacts with the SDS micelles as proposed, translational diffusion coefficients were measured by pulsed field gradient NMR. From these experiments it could be concluded that the catalyst is fully incorporated in the micelles at concentrations equal to those used in the catalytic reaction (see publication V for further details).

Table 13. Substrate scope in ATH of aryl alkyl ketones using ligand **45**.[a]

Entry	Substrate	Conversion [%][b]	ee [%][b]
1		97	97 (*R*)
2		94	95 (*R*)
3		99	76 (*R*)
4		98	96 (*R*)
5		97	97 (*R*)
6		97	96 (*R*)
7		96	94 (*R*)
8		86	96 (*R*)
9		96	97 (*R*)
10		74	78 (*R*)

[a] Reduction of 1 mmol substrate using $[RhCp^*Cl_2]_2$ and ligand **45** (S/C 100/1) together with 5 equiv. HCOONa and 10 mol% SDS in 2.5 mL distilled H_2O for 17 h. [b] Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB).

5. Concluding remarks

A novel class of ligands was developed for Rh-catalyzed asymmetric transfer hydrogenation in 2-propanol. Amino acid-derived hydroxamic acids were synthesized and employed in the reduction of aryl alkyl ketones, and were found to efficiently generate products of high enantioselectivity. Ligands based on amino acids are attractive to use as chiral inducers in catalysis, since they have a simple and versatile structure, and are prepared from inexpensive and easily accessible starting materials. This major advantage should be taken into consideration when comparing the results obtained using the hydroxamic acid-based catalysts with other well-established catalyst systems; the selectivities of the reductions are often equally high, whereas the activities are typically somewhat lower.

Another category of ligands, namely amino acid-derived thioamides, were moreover studied and further developed for ATH in 2-propanol. The same level of selectivity was obtained after a structural simplification of the original ligand structure, where the stereocenter at the amino acid C-terminus could be omitted and simply replaced by larger aromatic substituents in the same position. Employing the thioamides as ligands in the reduction of aryl alkyl ketones generated products of opposite configuration as compared to the use of hydroxamic acid-based catalysts.

A mechanistic investigation was performed on the Rh-hydroxamic acid/thioamide-catalyzed ATH-reaction to elucidate what caused the observed enantioswitch. Differently substituted and functionalized hydroxamic acid and thioamide ligands were prepared and evaluated in the reduction of acetophenone in 2-propanol, from which it could be concluded that the two ligands coordinate to the metal in a diverse fashion. A kinetic study was furthermore executed, where initial rates were measured at various substrate and donor concentrations. A difference in the rate determining step was found in the reactions catalyzed by the two complexes. This finding can be compared to the structurally similar Noyori catalyst (Ru-TsDPEN). The Noyori catalyst shows the same behavior in the 2-propanol system as the hydroxamic acid-containing complex, where the initial metal hydride formation is rate limiting. The reaction catalyzed by the thioamide complex on the other hand has the subsequent ketone reduction as the rate determining step. In addition to the initial rate measurements, rate constants were calculated for the forward and reverse reactions in each step of the overall reduction process.

Catalysts were also developed for ATH in water, where non-protected amino acid-derived hydroxamic acids turned out to be efficient ligands that are compatible with aqueous conditions. In comparison to other catalyst systems, e.g. those containing variants of the TsDPEN ligand, the rate of the reaction is considerably lower. Nevertheless, the extended applicability of these low-molecular weight catalyst-generating hydroxamic acids further stresses the usefulness of this class of ligands. In addition to the hydroxamic acid ligands, the corresponding amino acid amides were prepared and evaluated in the same reaction.

Finally, a modified TsDPEN ligand was used in the Rh-catalyzed ATH of dialkyl ketones in water. Surfactants were added to the catalytic reaction for the formation of micelles that can provide a reaction site and give rise to increased substrate stabilization. This catalyst system was moreover highly selective and efficient in the reduction of aryl alkyl ketones.

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Appendix I

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Appendix II

The contribution by the author to each publication is clarified below:

I: The author synthesized some of the ligands, did all characterizations and performed a substrate screen.

II: The author synthesized some of the ligands, did some characterizations, performed the initial and final catalytic experiments and supervised a diploma, who contributed with the major experimental part. The author wrote the publication.

III: The author performed almost all experiments and characterizations and wrote parts of the publication.

IV: The author performed all experiments and characterizations and wrote the major part of the publication.

V: The author performed all experiments except from the translational diffusion NMR measurements.