A Simple and Efficient Catalyst System for the Asymmetric Transfer Hydrogenation of Ketones

Katrin Ahlford, Alexey B. Zaitsev, Jesper Ekström, Hans Adolfsson*

Department of Organic Chemistry, Stockholm University, the Arrhenius Laboratory, 106 91 Stockholm, Sweden
Fax +46(8)154908; E-mail: hansa@organ.su.se

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Abstract: Aryl alkyl ketones are efficiently and selectively reduced (up to 97% ee) under transfer-hydrogenation conditions in 2-propanol using rhodium catalysts based on readily available amino acid derived hydroxamic acid ligands.

Key words: asymmetric catalysis, hydrogen transfer, reductions, rhodium, ketones

Asymmetric transfer hydrogenation (ATH) of ketones is a convenient method for the preparation of chiral secondary alcohols.[1] The method employs inexpensive and safe hydrogen donors such as simple secondary alcohols (e.g., 2-propanol) or formic acid (most often as sodium formate or the formic acid triethylamine azeotrope), instead of more hazardous and less conveniently handled molecular hydrogen. A significant progress in the field of ATH with respect to the development of new catalysts and ligands was achieved during the last decade. The introduction of catalysts based on ruthenium, rhodium, or iridium resulted in major improvements concerning the activity and selectivity of the reduction process.[2]

We have previously reported on pseudo-dipeptides and thioamides derived from Boc-protected amino acids as efficient ligands for the ATH of aromatic ketones employing Ru or Rh half-sandwich complexes (Figure 1).[3–5] These ligands feature no intrinsically basic nitrogen centers which is the case with the classical ligands used in this process, i.e. amino alcohols and monosulfonated diamines.

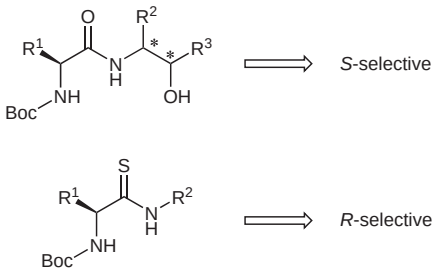

Figure 1 Stereochemical outcome of ATH catalyzed by Ru or Rh complexes of pseudo-dipeptide and thioamide ligands, respectively

The major topological difference between the two classes of ligands presented in Figure 1 is their potential denticities. Whereas the pseudo-dipeptides have the possibility to coordinate the metal with the carbamate, the central amide and the hydroxyl functionality, the thioamides can only act as bidentate ligands. We know from previous studies that in the case of the pseudo-dipeptides, all three functionalities are of utmost importance for the activity of the catalytic system, and furthermore, the possibility to deprotonate the central amide of the ligand is most crucial. To increase stability of the catalysts derived from the pseudo-dipeptides we focused on improving their coordinating ability. An obvious change was to decrease the pK_a of the central amide, thereby facilitating an easy deprotonation which would result in stronger coordination. Thioamides are considerably more acidic than the corresponding amides and exchanging oxygen for sulfur in the central amide functionality of a pseudo-dipeptide resulted in a ligand with significantly different properties.[4] When a ruthenium complex containing this thio-pseudo-dipeptide ligand was employed as catalyst in ATH, a switch of product enantioselectivity was observed. Hence, employing catalysts based on pseudo-dipeptide ligands derived from L-amino acids typically resulted in the formation of enantioenriched *S*-alcohols, whereas when the corresponding thioamide ligand was used, the *R*-alcohol was the major isomer. Moreover, we found that the alcohol functionality was no longer required and good catalytic activity and selectivity was obtained with the structurally simpler compound.

To investigate whether this enantioswitchable behavior is a consequence of the ligand acidity we decided to affect the acidity of the amide NH bond by changing the substitution pattern on the amide nitrogen rather than replacing the carbonyl oxygen by sulfur. We figured that the introduction of an electron-withdrawing substituent on the amide nitrogen would lead to a more acidic NH bond, a situation similar to the thioamide case, and the choice fell on one of the most simple derivatives fulfilling this criteria, namely the hydroxamic acid. In the field of asymmetric catalysis, hydroxamic acids have been successfully employed predominantely in oxidation reactions using early transition metals (e.g. vanadium).[6] However, herein we report on the efficient Rh-catalyzed ATH of ketones employing a novel set of *N*-Boc-protected amino acid ligands containing the hydroxamic acid functionality.

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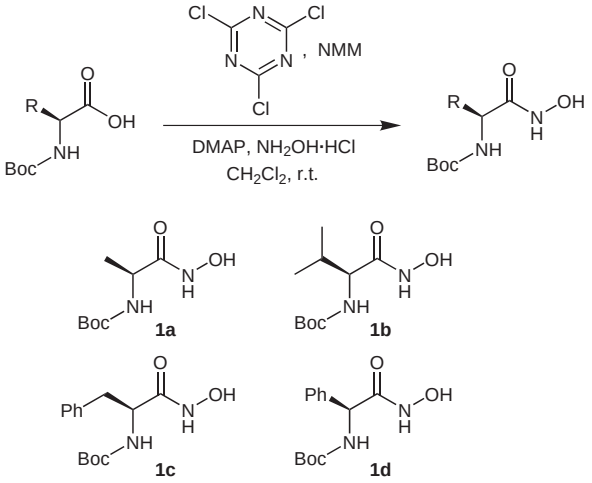
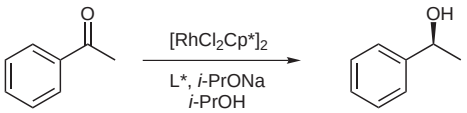
Hydroxamic acid ligands **1a–d** were prepared using the one-pot procedure introduced by Giacomelli and co-workers, starting from the appropriate *N*-Boc-protected amino acids (Scheme 1).[7] Unfortunately, we were not able to reproduce the yields reported in the Giacomelli paper, and in our hands the method gave a maximum yield of 40%, even though we were using a modified procedure provided to us by the authors.[8]



Scheme 1 One-pot procedure for the formation of hydroxamic acid ligands

Nevertheless, the hydroxamic acid ligands **1a–d** were evaluated in the rhodium-catalyzed ATH of acetophenone in 2-propanol using 0.5 mol% catalytic loading (Table 1). The rhodium catalysts were formed in situ by mixing $[RhCl_2Cp^*]_2$, ligand and sodium isopropoxide in 2-propanol. The amount of base turned out to be crucial and using a ratio of base to catalyst below 3 gave no conversion to the product.[9] Increasing the amount of base to 5 mol% resulted, however, in high conversions and ee using hydroxamic acids **1a–c** (Table 1, entries 1, 5, and 9).[10] Most interestingly, in contrast to ATH reactions performed with catalysts based on thioamide ligands (Figure 1), we found that 1-phenylethanol was formed with opposite configuration employing these simple hydroxamic acid ligands. The turnover frequency was slightly higher for the catalyst derived from ligand **1a** (TOF = 264 h^{-1}) as compared to catalysts formed with ligands **1b** and **1c** (TOF = 220 and 180 h^{-1}, respectively).[11] The selectivity was on the other hand somewhat better using ligands **1b** or **1c**. The use of the phenylglycine-derived ligand **1d** gave good conversion, although with low enantioselectivity (Table 1, entry 11). We have previously reported that addition of lithium chloride as a co-catalyst to the ATH system can have beneficial effects on both catalyst activity and selectivity.[3d,4] Accordingly, the addition of LiCl (5 mol%) to the reaction mixture led to a substantial increase of the reaction performance, and up to 97% ee was obtained for 1-phenylethanol using the valine-derived ligand **1b** (Table 1, entry 6). Interestingly, when the $[RuCl_2(p\text{-cymene})]_2$ complex, normally an efficient precatalyst together with amino alcohol, monotosylated diamine or pseudo-dipeptide ligands in the ATH of aryl alkyl ketones, was employed as a metal source, a considerably poorer result was obtained (Table 1, entry 3).

Table 1 *N*-Hydroxyl Amides of *N*-Boc-Protected Amino Acids as Ligands for the Rhodium-Catalyzed ATH of Acetophenone in 2-Propanol[a]

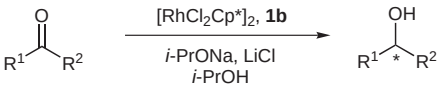


Entry	Ligand	LiCl (5 mol%)	Time (h)	Conv. (%)[b]	ee (%, conf.)[b]
1	**1a**	–	0.5	66	82 (*S*)
2	**1a**	+	0.5	56	88 (*S*)
3[c]	**1a**	–	0.5	4	71 (*S*)
4	**1b**	–	0.5	55	85 (*S*)
5	**1b**	–	2	89	87 (*S*)
6	**1b**	+	0.5	45	97 (*S*)
7	**1b**	+	2	82	97 (*S*)
8[d]	**1b**	–	2	89	87 (*S*)
9	**1c**	–	2	45	86 (*S*)
10	**1c**	+	2	63	92 (*S*)
11	**1d**	–	2	95	12 (*S*)

[a] Reaction conditions: acetophenone (1 equiv, 0.2 M in *i*-PrOH), $[\{RhCl_2Cp^*\}_2]$ (0.25 mol%), ligand (0.55 mol%) and *i*-PrONa (5 mol% unless otherwise indicated), r.t.
[b] Conversion and enantioselectivity were determined by GLC (CP Chirasil DEXCB).
[c] $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.25 mol%) was employed as catalyst precursor.
[d] The substrate was added 10 min after mixing the other reaction components.

From the results obtained in the ligand screening we found that the catalytic system containing the Rh catalyst based on the valine-derived ligand **1b** in combination with LiCl as co-catalyst showed overall superior activity and selectivity. Employing this catalyst mixture we studied the scope of the reaction and the results are presented in Table 2. As seen in Table 2, a range of differently substituted acetophenones were efficiently reduced with up to 99% conversion and up to 97% enantioselectivity using 0.5 mol% catalyst loading. The enantioselectivities obtained using this novel catalytic system are clearly compatible to our previously reported results employing pseudo-dipeptide-derived catalysts as well as to other known catalytic systems. The major advantage with the hydroxamic acid ligands is their simple preparation and most importantly readily available and inexpensive starting materials, which make this system highly competitive in comparison to other ATH protocols.

Table 2 Substrate Scope of the Rhodium-*N*-hydroxyl Amide Catalyzed ATH[a]



Entry	R^1	R^2	Time (h)	Convn (%)[b]	ee (%, conf.)[b]
1	Ph	Me	2	82	97 (*S*)
2	4-BrC_6H_4	Me	2	93	92 (*S*)
3	3-BrC_6H_4	Me	2	98	96 (*S*)
4	2-BrC_6H_4	Me	2	77	94 (*S*)
5	3-$CF_3C_6H_4$	Me	2	99	95 (*S*)
6	4-$MeOC_6H_4$	Me	2	54	81 (*S*)
7	3-$MeOC_6H_4$	Me	2	90	86 (*S*)
8	2-$MeOC_6H_4$	Me	2	85	90 (*S*)
9	Ph	Et	2	84	87 (*S*)

[a] Reaction conditions: substrate (1 equiv, 0.2 M in *i*-PrOH), [{$RhCl_2Cp^*$}$_2$] (0.25 mol%), ligand (0.55 mol%), LiCl (5 mol%) and *i*-PrONa (5 mol% unless otherwise indicated), r.t.
[b] Conversion and enantioselectivity were determined by GLC (CP Chirasil DEXCB).

The observed stereochemical outcome using rhodium catalysts based on amino acid derived hydroxamic acids was indeed unpredicted. As described above, in our previous report on the use of thioamides derived from *N*-Boc-protected amino acids in the ATH of acetophenone we achieved high conversion and enantioselectivity of (*R*)-1-phenylethanol using ligand **2a** (Figure 2).[4] Using the diastereomeric ligand **2b** gave the same product absolute configuration which show that the stereocenter present in the amino acid apparently is directing the outcome of the ATH reaction, presumably via the selective formation of a dominant rhodium hydride. However, as presented in this study, the use of the corresponding valine-derived hydroxamic acid ligand **1b** resulted in a product with slightly higher ee, albeit with opposite absolute configuration (Table 1, entry 6).

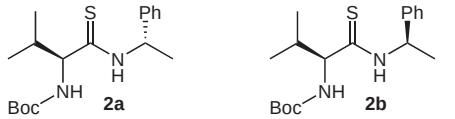


Figure 2 Rhodium-catalyzed ATH of acetophenone using thioamide ligands **2a** and **2b**

Consequently, the same *N*-Boc-protected amino acid can by simple procedures be transformed into ligands, which selectively give either *S*- or *R*-products in the ATH of aryl alkyl ketones.

However, the outcome of the rhodium-catalyzed ATH process using differently functionalized amino acids cannot simply be explained by the NH acidity of the ligand. Evidently, the coordination properties between ligands **1** and **2** are different, but at this point we are not able to pinpoint the reason for the observed enantioswitchable nature of the catalysts formed from these compounds. We are currently investigating this highly interesting feature and hope to be able to present results on this in due time.

In conclusion, we have introduced a new class of efficient ligands for the rhodium-catalyzed ATH of aryl alkyl ketones in 2-propanol. The ligands are easily accessed starting from commercially available *N*-Boc-protected amino acids. In addition we have demonstrated that enantioswitchable catalysts can be prepared from the same amino acid depending on the choice of functionalities introduced in the ligands. This feature can be most attractive in enantioselective catalysis when only one enantiomer of the precursor of the chiral ligand is available. We are currently investigating the reason behind the enantioswitchable nature observed using catalysts derived from differently substituted amino acid ligands in the asymmetric transfer hydrogenation of ketones.

Acknowledgment

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(8) **General Procedure for the Preparation of Hydroxamic Acid Ligands 1a–d**
To a solution of 2,4,6-trichloro-1,3,5-triazine (0.1 mmol) in anhyd CH_2Cl_2 (8 mL) cooled to 0 °C, the following components were added in the order they are written: Boc-protected amino acid (3 mmol), NMM (6 mmol), DMAP (0.3 mmol), and $NH_2OH{\cdot}HCl$ (3 mmol). The reaction mixture was stirred at r.t. for 14 h and thereafter filtered through a plug of silica, using EtOAc as eluent. The residue obtained after evaporation of the filtrate was chromatographed on silica (EtOAc–pentane, 10:1), followed by recrystallization from acetone–pentane to give the hydroxamic acids.
Compound **1a**: yield 41%. ^{1}H NMR (400 MHz, acetone-d_6, 25 °C): δ = 10.09 (s, 1 H), 8.22 (br s, 1 H), 6.06 (s, 1 H), 4.08 (q, *J* = 7.11 Hz, 1 H), 1.40 (s, 9 H), 1.29 (d, *J* = 7.11 Hz, 3 H). ^{13}C NMR (100 MHz, acetone-d_6, 25 °C): δ = 170.0, 155.1, 78.3, 47.7, 27.5, 17.8.
Compound **1b**: yield 25%. ^{1}H NMR (400 MHz, acetone-d_6, 25 °C): δ = 10.18 (br s, 1 H), 8.22 (br s, 1 H), 5.91 (d, *J* = 8.16 Hz, 1 H), 3.75–3.85 (m, 1 H), 1.40 (s, 9 H), 0.89–0.94 (m, 6 H). ^{13}C NMR (100 MHz, acetone-d_6, 25 °C): δ = 168.4, 155.4, 78.2, 57.5, 30.8, 27.5, 18.5, 17.6.
Compound **1c**: yield 25%. ^{1}H NMR (400 MHz, acetone-d_6, 25 °C): δ = 10.20 (br s, 1 H), 8.37 (br s, 1 H), 7.16–7.31 (m, 5 H), 6.12 (d, *J* = 7.32 Hz, 1 H), 4.23–4.36 (m, 1 H), 3.10 (dd, *J* = 13.71, 6.03 Hz, 1 H), 2.91 (dd, *J* = 13.71, 8.59 Hz, 1 H), 1.33 (s, 9 H). ^{13}C NMR (100 MHz, acetone-d_6, 25 °C): δ = 168.4, 155.1, 137.5, 129.2, 128.1, 126.3, 78.4, 53.6, 38.1, 27.5.
Compound **1d**: yield 10%. ^{1}H NMR (400 MHz, acetone-d_6, 25 °C): δ = 10.39 (br s, 1 H), 8.25 (br s, 1 H), 7.42–7.47 (m, 2 H), 7.26–7.37 (m, 3 H), 6.46 (d, *J* = 6.10 Hz, 1 H), 5.20 (d, *J* = 6.10 Hz, 1 H), 1.39 (s, 9 H). ^{13}C NMR (100 MHz, acetone-d_6, 25 °C): δ = 167.3, 154.7, 138.9, 128.3, 127.6, 127.0, 78.6, 55.7, 27.5.

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(10) **General Procedure for the Transfer Hydrogenation of Ketones Using Ligands 1a–d**
[{$RhCl_2Cp^*$}$_2$] (0.0025 mmol), ligand (0.0055 mmol), and LiCl (0.05 mmol) were dried under vacuum in a dry Schlenk tube for 15 min. Ketone (1 mmol), *i*-PrOH (4.5 mL), and a 0.01 M solution of *i*-PrONa in *i*-PrOH (0.5 mL, 5 mol%) were added under nitrogen. The reaction mixture was stirred at ambient temperature. Aliquots were taken after the reaction times indicated in Tables 1 and 2 and were then passed through a pad of silica with EtOAc as the eluent. The resulting solutions were analyzed by GLC (CP Chirasil DEXCB).

(11) Turnover frequencies determined after 30 min reaction time.