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Short Communication

Amino acid derived amides and hydroxamic acids as ligands for asymmetric transfer hydrogenation in aqueous media

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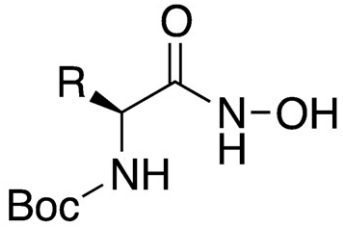
ABSTRACT

Amides and hydroxamic acids derived from α-amino acids were evaluated as ligands in combination with rhodium and iridium half-sandwich complexes in asymmetric transfer hydrogenation (ATH) of ketones. The reactions were performed in aqueous media using lithium formate as hydride source. The catalyst systems turned out to be highly efficient and ee's up to 90% were obtained.

1. Introduction

Chiral secondary alcohols are key intermediates in the industrial production of several important fine chemicals [1]. An efficient and straightforward route towards the formation of enantiomerically enriched alcohols is the reduction of the corresponding prochiral ketones. Asymmetric transfer hydrogenation (ATH) has proven to be an efficient, mild and highly selective method for this particular transformation. A further advantage is that hazardous molecular hydrogen or highly reactive hydride reagents can be avoided [2–4]. The ATH reaction is commonly conducted in alcoholic media, among which 2-propanol is the classical example [5,6]. Conveniently, the solvent also acts as the hydrogen donor. The reaction can furthermore be performed in formic acid or variants thereof, where the most common examples are the triethylamine/formic acid azeotrope (TEAF) and alkali formate-salts in water. However, the number of efficient catalyst systems that are compatible with these conditions are rather limited [7]. The combination of $[Ru(p\text{-cymene})Cl_2]_2$ together with the monotosylated diamine ligand 1,2-diphenyl-1,2-diaminoethane (TsDPEN) developed by Noyori, is an exception, since it is highly efficient in all reaction media mentioned above [8,9]. Previously, we have reported that *N*-Boc-protected amino acid derived hydroxamic acids (**1**) are excellent chiral mediators in the rhodium catalyzed ATH [10,11] in 2-propanol [12–15]. The modular nature of these ligands, in combination with easily accessible chiral starting material (i.e. amino acid building blocks), make them highly attractive for asymmetric catalysis. Ligands containing amino acid moieties have been widely explored in recent years by us [16–19] as well as by other research groups [20–25].



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The use of formic acid or a formate salt as hydride donor in ATH is most advantageous since the reductions thereby can be performed under seemingly irreversible conditions. However, when the valine based ligand **1** (R = isopropyl) was used together with $[RhCp^*Cl_2]_2$ as catalyst for the reduction of acetophenone using sodium formate as hydride donor and water as solvent, poor conversion of the starting material was observed (Table 1, entry 1). Most likely, the *N*-protecting group on **1** in combination with the aqueous media restricts the ligand from forming a catalytically active complex. We therefore decided to evaluate the deprotected versions of our hydroxamic acid ligands using the abovementioned conditions, and found to our delight that they efficiently catalyze the ATH reaction also in aqueous media. A

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modular low molecular weight catalyst system of this kind is of course highly attractive and the applicability is herein further extended. In addition to hydroxamic acid based ligands, we decided to investigate and compare the catalytic performance of the structurally even simpler amino acid amides. Faller and Lavoie previously reported that ruthenium-arene- and rhodium-arene complexes of L-prolineamide catalyze the reduction of ketones under transfer hydrogenation conditions using 2-propanol as solvent/hydride donor [26]. Furthermore, other ruthenium and rhodium amino acid amide complexes have previously been evaluated as catalysts for ATH of ketones in the formate/water system [27–31].

2. Experimental

2.1. General procedure for the asymmetric transfer hydrogenation of ketones catalyzed by $[RhCp^*Cl_2]_2$ and L-proline amide **4**

$[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol) and L-proline amide **4** (1.14 mg, 0.01 mmol) were evacuated together with SDS (29 mg, 0.1 mmol) and $HCOOLi \times H_2O$ (350 mg, 5 mmol) in a Schlenk tube for 10 min. Degassed distilled water (2.5 mL) was added to the tube under nitrogen atmosphere after which the ketone (1 mmol) was added, and thereafter the reaction mixture was stirred at 35 °C for 18 h. The reaction was quenched by addition of EtOAc (2.5 mL) to the reaction mixture after which aliquots were taken from the organic phase and passed through a pad of silica using EtOAc as eluent. The resulting solutions were analyzed by GLC (CP Chirasil DEXCB).

2.2. General procedure for the asymmetric transfer hydrogenation of ketones catalyzed by $[RhCp^*Cl_2]_2$ and L-proline hydroxamic acid **6**

$[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol) and L-proline hydroxamic acid **6** (1.3 mg, 0.01 mmol) were evacuated together with SDS (29 mg, 0.1 mmol) and $HCOOLi \times H_2O$ (350 mg, 5 mmol) in a Schlenk tube for 10 min. Degassed distilled water (2.5 mL) was added to the tube under nitrogen atmosphere after which the ketone (1 mmol) was added, and thereafter the reaction mixture was stirred at 24 °C for 14 h. The reaction was quenched by addition of EtOAc (2.5 mL) to the reaction mixture after which aliquots were taken from the organic phase and passed through a pad of silica using EtOAc as eluent. The resulting solutions were analyzed by GLC (CP Chirasil DEXCB).

2.3. General procedure for the asymmetric transfer hydrogenation of ketones catalyzed by $[IrCp^*Cl_2]_2$ and L-proline hydroxamic acid **6**

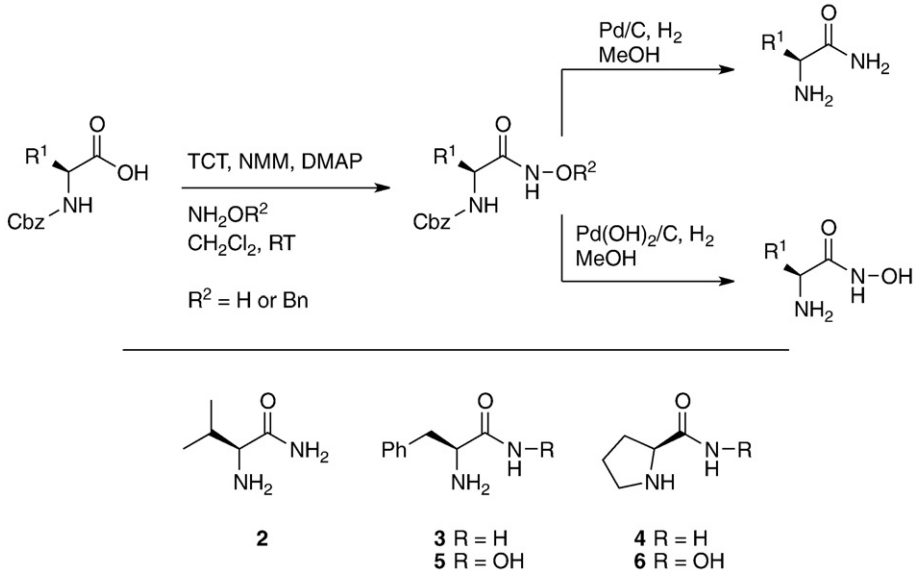
$[IrCp^*Cl_2]_2$ (4 mg, 0.005 mmol) and L-proline hydroxamic acid **6** (1.3 mg, 0.01 mmol) were evacuated together with SDS (29 mg, 0.1 mmol) and $HCOOLi \times H_2O$ (350 mg, 5 mmol) in a Schlenk tube for 10 min. Degassed distilled water (2.5 mL) was added to the tube under nitrogen atmosphere after which the ketone (1 mmol) was added, and thereafter the reaction mixture was stirred at 24 °C for 14 h. The reaction was quenched by addition of EtOAc (2.5 mL) to the reaction mixture after which aliquots were taken from the organic phase and passed through a pad of silica using EtOAc as eluent. The resulting solutions were analyzed by GLC (CP Chirasil DEXCB).

3. Results and discussion

Amino acid amide ligands **2**–**4** and hydroxamic acid ligands **5**–**6** were readily prepared according to Scheme 1 [32]. Both the amide and the hydroxamic acid can conveniently be obtained from the same protected hydroxamic acid intermediate, which in turn was prepared by coupling of the corresponding Cbz-protected amino acid with hydroxylamine or *O*-benzylhydroxylamine. As illustrated in Scheme 1, the choice of catalyst used in the hydrogenation/deprotection step determined which product class was obtained. Hence, hydrogenolysis using Pd/C resulted in the formation of amino acid amides, and for the preparation of the corresponding hydroxamic acid, $Pd(OH)_2/C$ was used [33]. It should be noted that attempts to prepare the hydroxamic acid from valine using this strategy failed, and regardless of catalyst used we obtained the primary amide.

With the set of ligands in hand we started to optimize the reaction conditions using acetophenone as a substrate, and with the isoelectronic complexes $[RhCp^*Cl_2]_2$ and $[IrCp^*Cl_2]_2$ as metal precursors (Table 1). The solubility of substrate and ligand/catalyst in water is rather poor, and as a standard procedure we choose to perform the reactions with SDS as additive.

Initially, the reaction was carried out using amide ligand **2** and sodium formate as reducing agent (entry 2, Table 1), however; the use



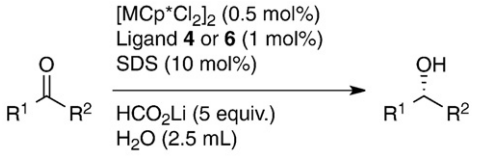
Scheme 1. Preparation of amino acid amides and hydroxamic acid ligands (**2**–**6**).

Table 1
Optimization of reaction conditions using ligands **2**–**6**.[a]

Entry	Metal	Ligand	Conversion [%][b]	ee [%][b]
1[c]	$[RhCp^*Cl_2]_2$	**1**	2	–
2[c]	$[RhCp^*Cl_2]_2$	**2**	99	46 (*R*)
3	$[RhCp^*Cl_2]_2$	**2**	96	52 (*R*)
4[d]	$[IrCp^*Cl_2]_2$	**2**	99	71 (*R*)
5	$[RhCp^*Cl_2]_2$	**3**	99	34 (*R*)
6	$[IrCp^*Cl_2]_2$	**3**	99	43 (*R*)
7	$[RhCp^*Cl_2]_2$	**4**	55	78 (*R*)
8[e]	$[RhCp^*Cl_2]_2$	**4**	80	77 (*R*)
9[f]	$[RhCp^*Cl_2]_2$	**4**	99	76 (*R*)
10	$[IrCp^*Cl_2]_2$	**4**	99	72 (*R*)
11	$[RhCp^*Cl_2]_2$	**5**	99	29 (*R*)
12[d]	$[RhCp^*Cl_2]_2$	**6**	99	69 (*R*)
13[c,d]	$[RhCp^*Cl_2]_2$	**6**	99	68 (*R*)
14[d]	$[IrCp^*Cl_2]_2$	**6**	99	74 (*R*)
15[d,g]	$[Ru(p\text{-cymene})Cl_2]_2$	**6**	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 reducing agent.
[d] 24 °C.
[e] 32 °C.
[f] 35 °C.
[g] 40 h.

of lithium formate resulted in higher selectivity (entry 3, Table 1). When employing $[IrCp^*Cl_2]_2$ as metal precursor, the selectivity was even further increased (entry 4, Table 1). The use of the sterically more demanding ligand **3** derived from phenylalanine did not improve the selectivity of the reaction (entries 5 and 6, Table 1), but it is again observed that the use of the iridium precursor gives slightly higher selectivity as compared to its rhodium counterpart. Ligand **4** on the other hand is less flexible in comparison to the other amino acid derived ligands, and should therefore result in a more strained chelate when coordinated to the metal [34]. The best results are indeed obtained when the rigid ligand **4** derived from proline is employed. Here, the opposite trend is observed and the best selectivity was measured with $[RhCp^*Cl_2]_2$ as the metal source, whereas the conversion was considerably lower in comparison to the use of the iridium-complex (entries 7 and 10, Table 1). Interestingly, the rhodium-catalyzed reaction did reach full conversion when the reaction mixture was left for 70 h, and the selectivity remained at 78% ee. In order to increase the rate of the rhodium-catalyzed reaction, a temperature variation investigation was performed to optimize the reaction conditions further. As expected, the selectivity decreases with increasing reaction temperature, however, most gratifyingly the decrease is only minor. The best balance between conversion, time and selectivity is obtained at 35 °C, where full



7 R^1 = Ph; R^2 = Me
8 R^1 = Ph; R^2 = Et
9 R^1 = 2-naphthyl; R^2 = Me
10 R^1 = 4'-Br-C_6H_4; R^2 = Me
11 R^1 = 3'-Br-C_6H_4; R^2 = Me
12 R^1 = 2'-Br-C_6H_4; R^2 = Me
13 R^1 = 4'-CF_3-C_6H_4; R^2 = Me
14 R^1 = 4'-NO_2-C_6H_4; R^2 = Me
15 R^1 = 4'-Me-C_6H_4; R^2 = Me
16 R^1 = 3',4',5'-triMeO-C_6H_2; R^2 = Me
17 R^1 = 3',5'-diMeO-C_6H_3; R^2 = Me
18 R^1 = 4'-MeO-C_6H_4; R^2 = Me
19 R^1 = 3'-MeO-C_6H_4; R^2 = Me
20 R^1 = 2'-MeO-C_6H_4; R^2 = Me
21 R^1 = *c*-hexyl; R^2 = Me

Scheme 2. Optimized reaction conditions, and ketones evaluated in the ATH.

conversion of acetophenone is obtained after 17 h. In comparison to reactions performed at lower temperature the selectivity of 1-phenylethanol only decreased to 76% ee (entry 9, Table 1). Further increase of the temperature to 40 °C led to lower enantioselectivity (73% ee). We next turned our attention towards the hydroxamic acid ligands **5** and **6**. The selectivities obtained using the hydroxamic acid ligands are in line with the corresponding amino acid amides and thus, the proline-derived hydroxamic acid ligand **6** gave the best results (entry 12, Table 1). The reaction went smoothly even at room temperature and full conversions were obtained using ligand **6** together with either iridium or rhodium (entries 12 and 14, Table 1). In contrast to the proline amide ligand **4**, superior selectivity was obtained with $[IrCp^*Cl_2]_2$ as compared to $[RhCp^*Cl_2]_2$. The use of the isoelectronic $[Ru(p\text{-cymene})Cl_2]_2$ complex as catalyst precursor led to low conversion and moderate ee (entry 15, Table 1). Summarizing the results presented in Table 1, it is obvious that the use of the proline-derived ligands (**4** and **6**) results in the most productive catalysts. The selectivity obtained in the reduction of acetophenone is similar regardless of metal precursor, and therefore we decided to pursue a comparative substrate screen using the rhodium complex of **4** and both the rhodium and iridium complexes of ligand **6**. Previous investigations have shown that different substrates may give rise to quite diverse results when screened with structurally similar catalysts [35]. In fact, the modularity and simplicity of the current ligand/catalyst system makes it ideal for such a multidimensional investigation.

A substrate screen was consequently performed under the optimized conditions, where differently functionalized and substituted acetophenones were reduced (Scheme 2 and Table 2). Substrates containing both electron rich and electron poor substituents were evaluated.

Regarding the proline amide derived catalyst, conversions are generally high or excellent, whereas the selectivity differs among the substrates evaluated. The best result is obtained with (3′-methoxy) acetophenone (**19**), which gives a conversion of 98% into the corresponding secondary alcohol and an ee of 88% (*R*). High selectivities are also obtained in the reduction of 2-acetonaphthone (**9**), (4′-trifluoromethyl)acetophenone (**13**) and (3′,5′-dimethoxy) acetophenone (**17**), where the ee's range from 80% to 85% in favor of the *R*-isomer. The use of the hydroxamic acid based catalysts resulted in excellent conversions for most substrates, even at shorter reaction time as compared to reactions performed with the amide catalyst (14

Table 2
Asymmetric transfer hydrogenation of ketones **7**–**21**.[a]

Ketone	**4**/$[RhCp^*Cl_2]_2$[b]		**6**/$[RhCp^*Cl_2]_2$[c]		**6**/$[IrCp^*Cl_2]_2$[c]	
	Conv. [%]	ee [%]	Conv. [%]	ee [%]	Conv. [%]	ee [%]
7	99	76 (*R*)	98	70 (*R*)	99	73 (*R*)
8	57	48 (*R*)				
9	82	85 (*R*)	73	83 (*R*)	99	90 (*R*)
10	97	69 (*R*)				
11	95	54 (*R*)	97	40 (*R*)	97	52 (*R*)
12	92	71 (*R*)	95	31 (*R*)	99	27 (*R*)
13	56	81 (*R*)	96	69 (*R*)	99	76 (*R*)
14	46	58 (*R*)				
15	59	78 (*R*)	76	90 (*R*)	86	80 (*R*)
16	94	76 (*R*)				
17	83	80 (*R*)	92	63 (*R*)	98	76 (*R*)
18	68	65 (*R*)				
19	98	88 (*R*)	95	62 (*R*)	96	76 (*R*)
20	73	73 (*R*)	81	rac	99	30 (*R*)
21	65	46 (*R*)				

[a] Reduction of 1 mmol substrate using $[MCp^*Cl_2]_2$ and ligand **4/6** (S/C 100/1) together with 5 equiv. HCOOLi and 10 mol% SDS in 2.5 mL distilled H_2O. Conversions and enantioselectivities were determined by GLC analysis (CP Chirasil DEX CB).
[b] Reactions performed at 35 °C for 18 h.
[c] Reactions performed at 24 °C for 14 h.

versus 18 h). Evidently, the reactions catalyzed by the hydroxamic acid derived complexes are more sensitive to substitution in the *ortho*-position of the substrate aryl-ring, as compared to the corresponding amide complexes. The selectivities are in general higher using the iridium precursor than with its rhodium counterpart, albeit for certain substrates higher selectivity was obtained using the latter catalyst. The best selectivity obtained using the iridium catalyst was in the reduction of 2-acetonaphthone (**9**) where the product was formed in 90% ee (*R*). Using the rhodium-based catalyst we obtained the same level of enantioselectivity (90%) in the reduction of (4′-methyl)acetophenone (**15**).

From the presented results it is apparent that the amino acid derived amides as well as hydroxamic acids are efficient ligands in the ATH reaction in aqueous media. Interestingly, there is a strong correlation between the amino acid side chain and the degree of selectivity obtained with catalysts from the two different ligand classes. Moreover, the selectivity-correlation is in agreement with the results obtained employing the parent amino acids as ligands together with $[RhCp^*Cl_2]_2$ under similar reaction conditions. Hence, the use of L-proline gives the best selectivity in the formation of 1-phenylethanol (76% ee (*R*)), with L-valine a 50% ee (*R*) is obtained, and using L-phenylalanine results in a merely 33% ee (*R*). It should be pointed out that the conversion was substantially lower (around 20%, reactions performed at ambient temperature) using the amino acid based catalysts. The correlation is interesting from a fundamental perspective, since an initial ligand screen can be performed with non-functionalized amino acids, rather than using more complex ligand structures. Similar levels of selectivity should be expected from the simpler catalyst systems, and these results can therefore act as a guideline in further ligand developments.

4. Conclusion

In summary, we have reported two classes of simple, low molecular weight ligands, namely amino acid derived primary amides and hydroxamic acids, that together with $[RhCp^*Cl_2]_2$ or $[IrCp^*Cl_2]_2$ are efficient and compatible catalysts for transfer hydrogenation not only in 2-propanol as previously published, but also in aqueous media. When using these ligands in the water/lithium formate/SDS system, conversions and selectivities are high for most of the substrates evaluated, proving the usefulness of these catalyst systems.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.03.032.

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