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Fine-tuning catalytic activity and selectivity—[Rh(amino acid thioamide)] complexes for efficient ketone reduction

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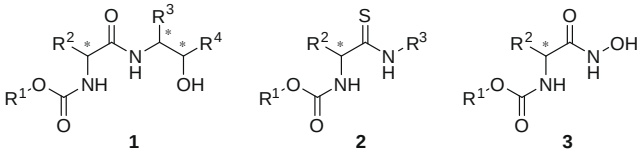
ABSTRACT

Amino acid-derived thioamides are prepared and evaluated as ligands in the rhodium-catalyzed asymmetric transfer hydrogenation of ketones in 2-propanol. It is found that increasing the steric bulk at the C-terminus of the ligand had a positive impact on both activity and selectivity in the reduction reaction. In order to find the optimum catalyst, a study is performed on a series of thioamide ligands having substituents of varying size.

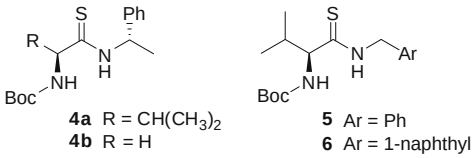
The enantioselective reduction of prochiral ketones has become a reaction of increasing importance, since the resulting enantioenriched secondary alcohols are key intermediates for the preparation of a large number of biologically active compounds.[1] Asymmetric transfer hydrogenation (ATH) has proven to be an efficient, mild and versatile method for this particular transformation, where the use of hazardous molecular hydrogen or highly reactive hydride reagents can be avoided.[2] A number of transition metal complexes have been found to efficiently catalyze the ATH reaction, where a 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 the most well-known catalyst to date.[3,4]

Previously, we have reported that amino acid-derived pseudodipeptides **1**, thioamides **2** and hydroxamic acids **3** in combination with Ru or Rh half-sandwich complexes are excellent catalysts for the ATH reaction.[5,6] Studies on ligand structure **2** indicated that an aromatic substituent at the C-terminus is most appropriate, and that increased steric bulk of this substituent could further enhance the catalyst performance, regarding both activity and selectivity. Herein we present the preparation of several amino acid thioamides bearing N-substituents of varying size as well as different electronic properties. These novel compounds were subsequently evaluated as ligands in the rhodium-catalyzed ATH reaction of ketones in 2-propanol.



1 **2** **3**

Previous studies on thioamides as ligands in the rhodium-catalyzed ATH, using different amino acid-derived thioamides, showed that the ligand **4a** prepared from valine gave the best results.[5g] Furthermore, the stereochemical outcome of the reaction was primarily correlated with the configuration of the amino acid part of the ligand. In fact, when employing ligand **4a** in the ATH reaction of acetophenone in 2-propanol, the resulting 1-phenylethanol was obtained in 88% conversion and 95% ee (*R*) after 30 min.[5g] When the corresponding glycine-derived ligand **4b** was employed, the catalytic activity was significantly reduced, and the selectivity was almost completely lost [31% conversion and 4% ee (*R*) after 120 min].[7] Conversely, the Rh-catalyst based on the valine-derived ligand **5** having a benzyl substituent at the C-terminus, resulted in somewhat reduced catalyst activity and selectivity [67% conversion and 86% ee (*R*) after 120 min], while the catalyst formed with **6** possessing a larger 1-naphthylmethyl substituent at the same position, that is, also lacking the stereocentre at the C-terminus, performed as equally well as Rh-**4a** (vide infra). Thus, the stereocentre at this part of the ligand can conveniently be omitted. In order to find out whether the substituent at the C-terminus had additional impact on the catalyst performance, further investigation was performed.



4a R = $CH(CH_3)_2$
4b R = H

5 Ar = Ph
6 Ar = 1-naphthyl

Ligands **6**–**13** were prepared and screened in the reduction of acetophenone using the reaction conditions presented in Scheme 1.[8] Catalysts based on all the ligands showed good activity and excellent

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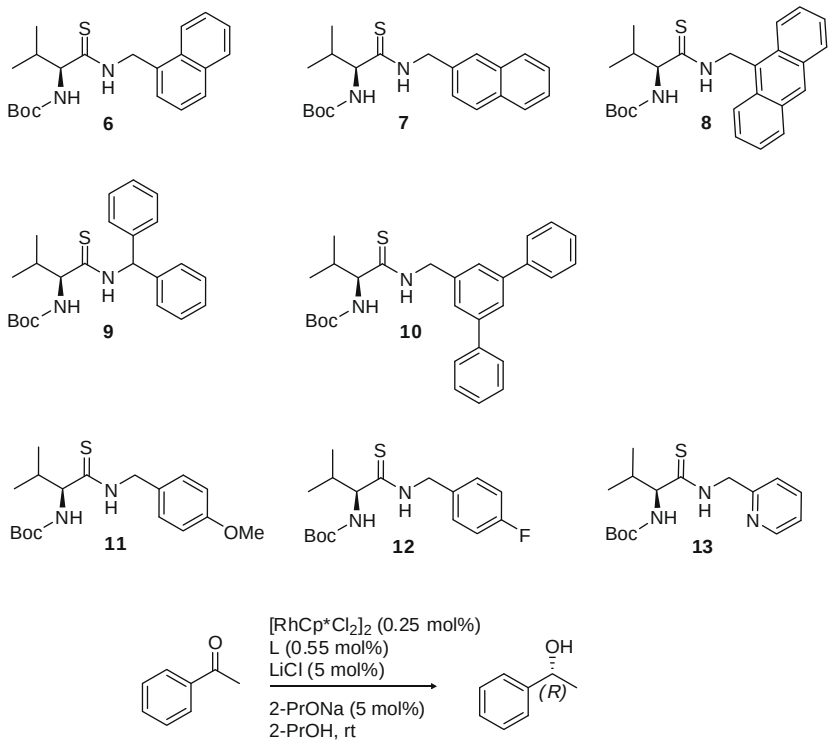


Scheme 1. Reaction conditions employed in the ATH of acetophenone.

selectivity, as can be seen in Table 1; ligand **7** appeared to be the most promising (Table 1, entry 2). Apparently, the increase of steric bulk at the C-terminus improved the catalyst performance but only to a certain extent. When employing the sterically demanding ligand **8**, derived from 9-(aminomethyl)anthracene, the selectivity was somewhat reduced (Table 1, entry 3), whereas using the more bulkier ligand **10** led to substantially lower activity even though the selectivity was retained (Table 1, entry 5). The use of ligands **11**–**13**, containing substituents with different electronic properties resulted in slightly poorer catalyst performance (Table 1, entries 6–8).

Traditionally, ligands or catalysts are screened with one benchmark substrate, of which the best-performing ligand/catalyst is further tested in a substrate-screen to evaluate the scope of the catalyst performance. In this manner, valuable information can be lost, since a certain catalyst can be the most suitable for a particular substrate, whereas it can be out-performed by other catalysts for different substrates. By performing a multiple screen containing ligands and substrates, it is possible to fine-tune the catalyst depending on the nature of the substrate.

Rh-catalysts based on ligands **6**–**9** and **13** were used in the reduction of various ketones, representing both electron-rich and electron-poor substrates. In addition, substrates having different degrees of potential steric hindrance on the aryl or the α-position were evaluated (Scheme 2 and Fig. 1).

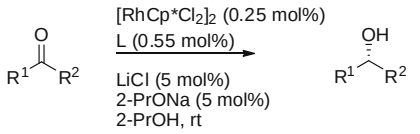
From the catalyst/substrate screen it was apparent that acetophenones substituted with electron-withdrawing groups (**14** and **15**) were readily reduced to the corresponding alcohols, whereas the electron-rich substrates reacted more slowly and with slightly lower selectivity (**16** and **17**). The catalytic reduction of 2,5-dimethoxyacetophenone (**17**) resulted in low activity using ligand **7** (8% conversion and 38% ee); however, when ligand **9** was used for the same substrate, the catalyst performance was considerably higher (49% conversion and 91% ee). As can be seen in Figure 1, substrate **18** was reduced by catalysts based on ligands **7** and **9**, in equally good results (91% conversion and 94% ee). In the reduction of 1-propiophenone (**19**), the best selectivity was obtained using ligand **7** (97% ee).

The overall best-performing ligand **7** was further evaluated in the reduction of more challenging substrates, including two dialkyl ketones (Scheme 3 and Table 2). The highest turnover frequency (TOF), 704 h^{-1} after 15 min (1152 h^{-1} after 5 min), was observed for 4-nitroacetophenone (**20**), (Table 2, entry 7).[10] 2-Fluoroacetophenone (**21**) reacted rather poorly, probably due to electronic effects (Table 2, entry 8). As previously observed for most ATH protocols, this catalyst system is evidently not appropriate for asymmetric reduction of dialkyl ketones, thus geranylacetone (**24**) is readily reduced, but with no selectivity (Table 2, entry 11).

Table 1
ATH of acetophenone using ligands **6**–**13**[a]

Entry	Ligand	*t* (min)	Conversion[b] (%)	ee[b] (%)
1	**6**	30	85	93
2	**7**	30	81	96
3	**8**	120	88	89
4	**9**	30	84	91
5	**10**	120	47	92
6	**11**	30	71	94
7	**12**	30	80	94
8	**13**	120	63	92

[a] Reaction conditions according to Scheme 1.
[b] Conversions and enantioselectivities were determined by GLC analysis (CP Girasil DEX CB).



14 R^1= 4-Br-C_6H_4, R^2= Me
15 R^1= 4-CF_3-C_6H_4, R^2= Me
16 R^1= 4-MeO-C_6H_4, R^2= Me
17 R^1= 2,5-diMeO-C_6H_3, R^2= Me
18 R^1= 1-naphthyl, R^2= Me
19 R^1= Ph, R^2= Et

Scheme 2. Reaction conditions employed in the ATH of substrates **14**–**19**.

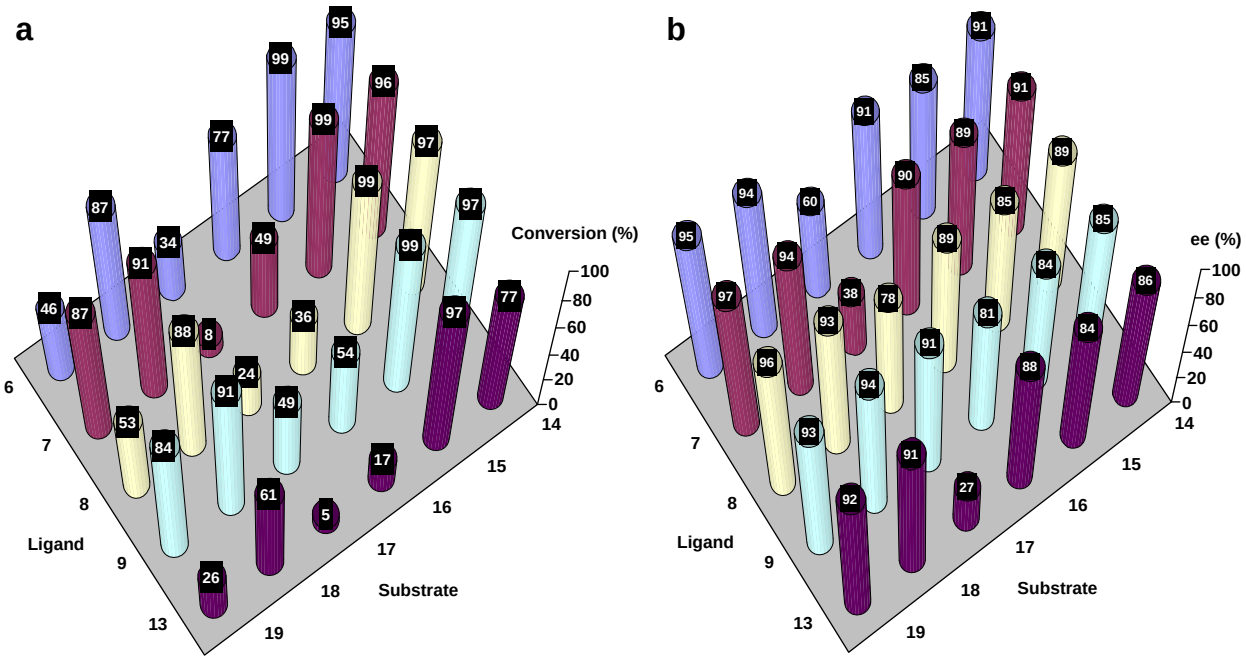
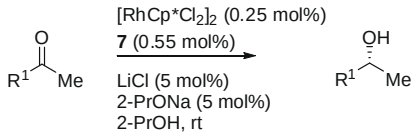


Figure 1. ATH of substrates **14**–**19** using rhodium catalysts derived from ligands **6**–**9** and **13**.[9] (a) Conversion; (b) enantioselectivity.



20 R^1= 4-NO_2-C_6H_4 **23** R^1= *c*-hexyl
21 R^1= 2-F-C_6H_4 **24** R^1=
22 R^1= 3-pyridyl

Scheme 3. Reaction conditions employed in the ATH of substrates **14**–**24**.

Table 2
ATH of substrates **14**–**24** using ligand **7**[a]

Entry	Substrate	*t* (min)	Conversion[b] (%)	ee[b] (%)
1	**14**	30	96	91
2	**15**	30	>99	89
3	**16**	30	49	90
4[c]	**17**	120	49	91
5	**18**	30	91	94
6	**19**	120	87	97
7[d]	**20**	15	88	78
8	**21**	120	73	59
9	**22**	120	6	n.d.
10	**23**	120	8	n.d.
11	**24**	120	93	*rac*

n.d. = not determined.
[a] Reaction conditions according to Scheme 3.
[b] Conversions and enantioselectivities were determined by GLC analysis (CP Girasil DEX CB).
[c] Result obtained with ligand **9**.
[d] Reaction mixture contains 1 mL of THF.

In summary, we have reported a highly efficient and selective catalyst system for the ATH of aryl alkyl ketones based on amino acid thioamide–rhodium complexes. The major advantages using this catalytic system are (1) high activity and selectivity for a number of different ketone substrates and (2) a simple and straightforward protocol for the preparation of highly modular amino acid-based ligands. Moreover, in comparison to our previously reported catalyst system based on ligand **4a**, the current study shows that excellent catalysts can be obtained using structurally simpler ligands containing only one stereogenic centre. From the multiple ligand- and substrate-screen performed, it was possible to find the optimum catalyst for a particular substrate.

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Supplementary data

Supplementary data (experimental procedures for ligand preparation, catalytic experiments along with ligand characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.116.

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8. See Supplementary data for detailed information on ligand formation.
9. Reaction conditions according to Scheme 2. Conversions and enantioselectivities were determined by GLC analysis (CP Girasil DEX CB). A table for Figure 1 is available in the Supplementary data.
10. 2-Propanol (1 mL) was exchanged for THF in order to dissolve the substrate.