ORGANIC LETTERS

2006
Vol. 8, No. 22
5129−5132

# Enantioswitchable Catalysts for the Asymmetric Transfer Hydrogenation of Aryl Alkyl Ketones

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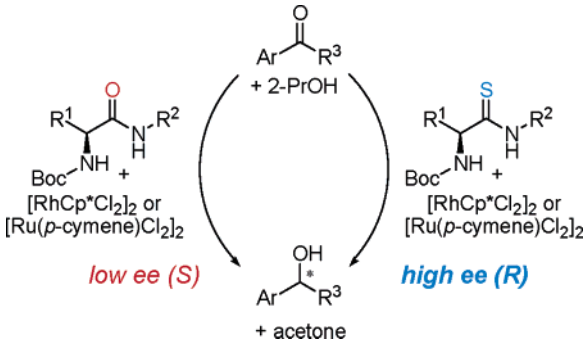
**Received September 8, 2006**

## ABSTRACT




**A subtle change in the ligand structure, replacing the carbonyl oxygen with sulfur in simple α-amino acid amides, resulted in a dramatic activity and selectivity improvement in the rhodium- or ruthenium-catalyzed reduction of ketones under hydrogen transfer conditions. In addition, in most cases, a switch of the product's absolute configuration was observed on going from amides to the corresponding thioamides. Under optimized conditions, we obtained the secondary alcohol products in high yield and enantioselectivity (up to 97% ee) using only 0.25 mol % catalyst loading.**

Herein, we describe the preparation and application of a novel set of simple yet highly modular ligands for rhodium- and ruthenium-catalyzed reduction of aryl alkyl ketones under transfer hydrogenation conditions. A minuscule change in the ligand structure had a dramatic influence on the activity and selectivity of the catalysts, and as a result, highly selective enantioswitchable catalysts were obtained from the same ligand backbone. Asymmetric transfer hydrogenation (ATH) is an important and convenient catalytic transformation allowing for easy preparation of enantiomerically enriched alcohols[1,2] and amines[2] from prochiral ketones and imines without any specialized pressure equipment. Further improvement of the catalytic activity and enantioselectivity of ATH is a continuing challenge. The mechanism-driven design[3] of new catalysts is the shortest way to better ATH processes. Ru(II) and Rh(III) half-sandwich complexes are generally thought to form active catalysts for ATH when combined with 1,2-amino alcohols or monotosylated 1,2-diamines, containing a basic primary or secondary amino

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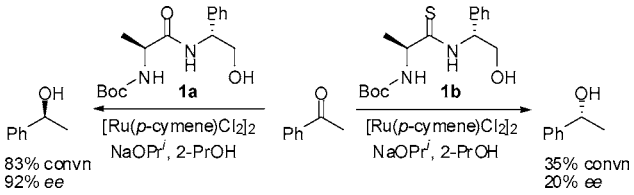
10.1021/ol062227q CCC: $33.50 
**Published on Web 09/27/2006**

group in the $\beta$-position to a relatively acidic OH or NH group. N-Protected amino acid hydroxy-amide ligands (**1a**) developed in our group[4] represent a different class of ligands without an explicit basic nitrogen center, for which alkali ions play a crucial role in the hydrogen transfer step.[5] Structural variation in these pseudodipeptides revealed that the presence of a secondary amide is necessary for high catalytic activity. In the active complex, the amide is deprotonated and acts as a coordinating counterion for the transition metal. To increase the stability of the catalytically active metal complex, we sought to substitute the amide functionality for a group of higher acidity. In the present communication, we report how a seemingly subtle change in the ligand structure, namely, replacement of the amide oxygen in Boc-protected amino acid amides by sulfur, and modification of the catalytic system with a lithium salt lead to a novel and most efficient class of Ru and Rh catalysts for the ATH of aromatic ketones in isopropanol. In addition, as illustrated in the catalytic experiments presented in Scheme 1, the replacement of the amide functionality for the corresponding thioamide resulted in a dramatic switch of the product enantioselectivity in the ATH.

**Scheme 1.** Switch of Enantioselectivity in the Reduction of Acetophenone

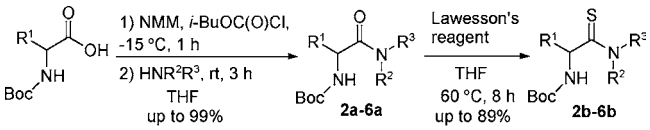



In the Ru(II) pseudodipeptide-catalyzed reduction of ketones, we have found a strong correlation between the product configuration and the stereocenters of the ligand. Even though the ligand possesses two stereogenic centers, the configuration of the amino acid part correlates well with the product configuration, and catalysts with ligands based on natural amino acids predominately favor the formation of *S*-alcohols. Therefore, the outcome of the reaction using the corresponding thioamide (**1b**) was most unexpected. In the reduction of acetophenone, the replacement of the central amide for a thioamide resulted in the formation of the secondary alcohol in 20% ee in favor of the *R*-product. Apparently, the slight change of the structure had a dramatic influence on the activity and selectivity of the formed catalyst. The thioamide was prepared from the corresponding *O*-TBS-protected pseudodipeptide using Lawesson's reagent. When the *O*-TBS-protected hydroxy-thioamide was employed as the ligand for Ru(II) in the reduction of acetophenone, we obtained (*R*)-1-phenylethanol in 51% conversion and in 50% ee. This result is in striking contrast to previous results achieved using pseudodipeptide ligands because any manipulation of the alcohol moiety resulted in no or low activity of the catalyst.

The increased catalytic activity observed using the potentially bidentate *O*-silylated hydroxy-thioamide ligand encouraged us to further investigate such ligands. A series of simple Boc-protected amino acid amides were prepared and subsequently converted into the corresponding thioamides.

Ligands **2b**−**6b** were accessed in good yields in two steps from commercially available Boc-protected amino acids (Scheme 2).

**Scheme 2.** Synthesis of the Thioamide Ligands




$R^1$ = Me, *i*-Pr, Ph; $R^2$ = H, Alk; $R^3$ = H, Alk

Recently, Pelagatti and co-workers reported on the catalytic activity of amino acid amides in the ATH of aromatic ketones in isopropanol.[6] At 90 °C, they achieved good conversions with ee's up to 47%, whereas the appropriate Boc-protected amides displayed no catalytic activity in the process. As a result of screening the thioamide ligands with different substitution patterns in the ATH of acetophenone (Table 1 and Supporting Information), we observed that the secondary amide NH function as well as the BocNH or $NH_2$ groups in the amino acid moiety are crucial for high catalytic activity. Ligand **2b** gave the highest enantioselectivity among the simple thioamides examined. The selectivity could be further increased to 92% ee by addition of LiCl (Ru/Li = 1:10) to the catalytic system. The optimal amount of base (*i*-PrONa) was 10 mol %, and the highest conversions were achieved when the base was added subsequent to all other components, including the substrate.

In analogy with the results obtained using the pseudodipeptides **1a** and **1b**, we observed in most cases a switch of the sign of enantioselectivity on going from amides to the appropriate thioamides (Table 1).

Screening catalysts derived from other metal precursors in the ATH of acetophenone using ligand **2b** revealed even higher activity and enantioselectivity of a catalyst based on $[\{RhCl_2Cp^*\}_2]$.[7] In this case, the addition of LiCl (Rh/Li = 1:10) led to a significant improvement of activity and enantioselectivity, and excellent results could be obtained

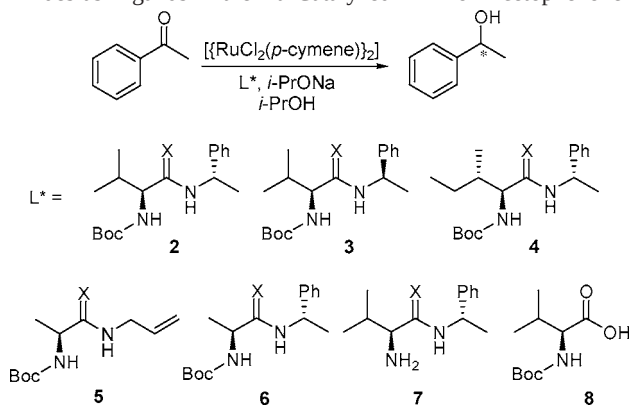
(3) For mechanistic aspects of transfer hydrogenations, see the following reviews: (a) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201−2237. (b) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237−248.

(4) (a) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun.* **2002**, 2046−2047. (b) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem.−Eur. J.* **2003**, *9*, 4031−4045. (c) Bøgevig, A.; Pastor, I. M.; Adolfsson, H. *Chem.−Eur. J.* **2004**, *10*, 294−302. (d) Västilä, P.; Wettergren, J.; Adolfsson, H. *Chem. Commun.* **2005**, 4039−4041. (e) Wettergren, J.; Bøgevig, A.; Portier, M.; Adolfsson, H. *Adv. Synth. Catal.* **2006**, *348*, 1277−1282.

(5) Västilä, P.; Zaitsev, A. B.; Wettergren, J.; Privalov, T.; Adolfsson, H. *Chem.−Eur. J.* **2006**, *12*, 3218−3225.

(6) (a) Pelagatti, P.; Carcelli, M.; Calbiani, F.; Cassi, C.; Elviri, L.; Pelizzi, C.; Rizzotti, U.; Rogolino, D. *Organometallics* **2005**, *24*, 5836−5844. (b) For another example of the use of amino acid amides in ATH, see: Faller, J. W.; Lavoie, A. R. *Organometallics* **2001**, *20*, 5245−5247.

**Table 1.** Boc-Amino Acid Thioamides vs the Appropriate Amides as Ligands in the Ru-Catalyzed ATH of Acetophenone[a]




| entry | ligand | X | time (h) | conversion (%)[b] | ee (%, conf)[b] |
|---|---|---|---|---|---|
| 1 | **2** | S | 2 | 49 | **81** (*R*) |
| 2 | | O | 2 | 5 | 0 |
| 3[c] | | S | 0.25 | 84 | **81** (*R*) |
| 4[c,d] | | S | 0.25 | 57 | **92** (*R*) |
| 5 | **3** | S | 2 | 64 | **78** (*R*) |
| 6 | | O | 2 | 4 | 0 |
| 7 | **4** | S | 2 | 47 | **81** (*R*) |
| 8 | | O | 2 | 3 | 0 |
| 9 | **5** | S | 2 | 46 | 42 (*R*) |
| 10 | | O | 2.5 | 20 | 11 (*S*) |
| 11 | **6** | S | 2 | 45 | 59 (*R*) |
| 12 | | O | 2 | 7 | 5 (*S*) |
| 13[e] | **7** | S | 0.25 | 68 | 58 (*R*) |
| 14[d,e] | | S | 0.25 | 74 | 59 (*R*) |
| 15 | **8** | | 2 | 7 | 15 (*S*) |

[a] Reaction conditions: acetophenone (1 equiv, 0.2 M in 2-propanol), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol %), ligand (1.1 mol %), and *i*-PrONa (5 mol % unless otherwise indicated), room temperature. [b] Conversion and enantioselectivity were determined by GLC (CP Chirasil DEXCB). [c] 10 mol % of *i*-PrONa was used. [d] 10 mol % of LiCl was added to the system. [e] A decreased amount of the catalyst (Ru/L/AcPh/base = 1:1.1:200:10) was used because at higher loadings erosion of enantioselectivity was observed due to the fast establishment of the equilibrium in the system.

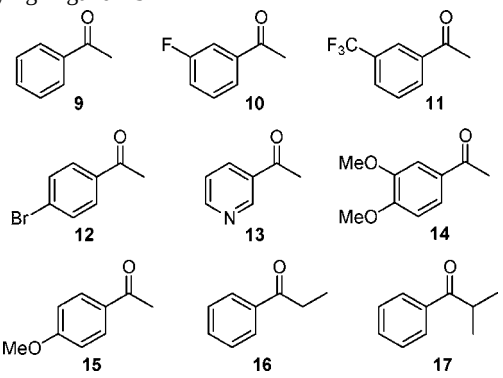
in the ATH of various aromatic ketones with only 0.25 mol % loadings of the Rh complex (Table 2).

Particularly good results were obtained with electron-poor substrates (Table 2, entries 2−4).

Reduction of *m*-trifluoromethylacetophenone, which constitutes a key step in the preparation of a commercial fungicide,[8] gave excellent conversion and enantioselectivity with only 0.125 mol % of the Rh complex (Table 2, entry 3). High enantioselectivities were obtained with substrates containing bulky alkyl substituents.

The switch of the sign of enantioselectivity on going from amides to the appropriate thioamides (Table 1) may arise from a different mode of coordination due to significant

**Table 2.** Rh(III)-Catalyzed ATH of Various Ketones, Employing Ligand **2b**[a]




| entry | substrate | time (h) | conversion (%)[b] | ee (%, conf)[b] |
|---|---|---|---|---|
| 1 | **9** | 0.5 | 88 | 95 (*R*) |
| 2 | **10** | 0.25 | 97 | 96 (*R*) |
| 3[c] | **11** | 0.5 | 98 | 96 (*R*) |
| 4 | **12** | 0.25 | 96 | 92 (*R*) |
| 5 | **13** | 2 | 33 | 95 (*R*) |
| 6 | **14** | 0.5 | 55 | 96 (*R*) |
| 7 | **15** | 0.5 | 56 | 91 (*R*) |
| 8 | **16** | 0.5 | 88 | 96 (*R*) |
| 9 | **17** | 2 | 61 | 97 (*R*) |

[a] Reaction conditions: ketone (1 equiv, 0.2 M in isopropanol), [{$RhCl_2Cp^*$}$_2$] (0.25 mol %), ligand (0.6 mol %), LiCl (5 mol %), and *i*-PrONa (5 mol %), room temperature. [b] Conversion and enantioselectivity were determined by GLC. [c] Rh/L/LiCl/AcPh/base = 1:1.1:10:400:10.

differences in the acidity of the NH functions in amides and carbamates relative to those in thioamides (Figure 1).[9]

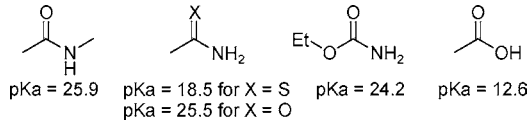



**Figure 1.** Representative p$K_a$ values of amides, carbamates, thioamides, and carboxylic acids (DMSO).

Thus, in the case of thioamides such as **2**, the thioamide NH bond can serve as the acidic site and the BocNH can serve as the basic one.

The higher activity observed at higher metal to base ratios can be rationalized by an increased tendency of thioamides to coordinate via the amide nitrogen at pH > 9, as was reported by Kowalik et al.[10] for the coordination of methionine *N*-methylthioamide to Cu(II). However, the acidity is not the only factor affecting catalytic activity. When Boc valine

(7) ATH using [{$RhCl_2Cp^*$}$_2$] and the corresponding amide **1a** resulted in 4% conversion to racemic 1-phenylethanol.

(8) Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process Res. Dev.* **2000**, *4*, 346−348.

(9) These data were extracted from the table at http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

(10) Kowalik, T.; Kozlowski, H.; Rolka, K.; Kupryszewski, G. *Proc. - Sch.-Symp. Inorg. Biochem. Mol. Biophys.* **1985**, 169−170.

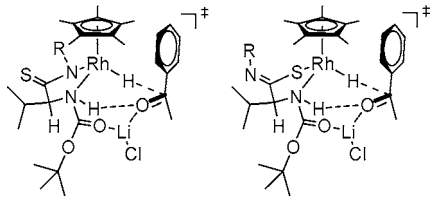


**Figure 2.** Proposed structures of the transition state of the hydrogen transfer.

(**8**), containing an acidic OH group (Figure 1), was employed as the ligand, we observed poor activity in the ATH (Table 1, entry 15). Therefore, coordination of thioamides through the sulfur atom cannot be excluded. Lithium cations obviously play a crucial role in the hydrogen transfer, assisting with substrate binding in the outer coordination sphere. The Boc group is likely to be involved in such a binding because the ATH with the deprotected ligand **7** (Table 1, entries 13 and 14) is relatively insensitive to the presence of LiCl. On the basis of the above observations, we propose that highly ordered transition states for the hydrogen transfer, taking into consideration the different coordination modes of the ligand, can be presented as in Figure 2.

In summary, we have developed a novel class of simple, modular, and highly efficient ligands for Ru- and Rh-catalyzed asymmetric transfer hydrogenation of aromatic ketones in isopropanol. A remarkable feature with these amino acid based compounds is the switch of product enantioselectivity observed when the amide functionality is replaced by the corresponding thioamide. In addition, the obtained results have significant mechanistic implications because they pinpoint the structural features which are essential for high catalytic activity and selectivity. Mechanistic investigations concerning the hydrogen transfer pathways in these catalytic systems are currently underway and will be published elsewhere.

**Acknowledgment.** We thank Professor Steven V. Ley of the University of Cambridge for valuable discussions. Support has been provided by the Swedish Research Council and the Wenner-Gren Foundation (postdoctoral fellowship to A.B.Z.).

**Supporting Information Available:** Additional results from ligand screening, experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062227Q