Catalysts for the Asymmetric Transfer Hydrogenation of Ketones Derived from L-Prolinamide and (p-CymeneRuCl$_2$)$_2$ or (Cp*RhCl$_2$)$_2$

J. W. Faller* and Adrien R. Lavoie

Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

Received July 19, 2001

Summary: The combination of L*-prolinamide with (p-CymeneRuCl$_2$)$_2$ or (Cp*RhCl$_2$)$_2$, in the presence of KOH/2-propanol, has been found to generate catalysts in situ that are capable of enantioselectively reducing aryl ketones to the respective (R)-alcohols. Furthermore, when the catalyst derived from (p-CymeneRuCl$_2$)$_2$/*L*-prolinamide was applied to the asymmetric reduction of 1′-tetralone at −24 °C, (R)-tetralol was produced in 93% ee.*

Introduction

Increasing numbers of effective catalysts (in terms of enantioselectivity, turnover number, and substrate compatibility) have been discovered; however, expensive chiral ligands are often required. When economic factors are involved, a common consensus is that amino acids are the ligands of choice.[1] Although amides of amino acids have not been largely exploited in catalysis, we anticipated that they might prove to be effective ligands in asymmetric transfer hydrogenations. As an initial step into the investigation of such ligands, we have examined L-prolinamide in combination with (p-CymeneRuCl$_2$)$_2$ and (Cp*RhCl$_2$)$_2$ for the asymmetric hydrogenation of α- and β-aryl ketones and herein report these results.[2,3]

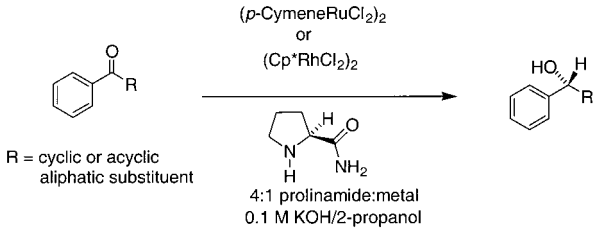

Figure 1. Generation of a catalyst in situ for the asymmetric hydrogenation of ketones.

Results and Discussion

Catalysts were prepared by heating (100 °C) the desired organometallic dimer (Ru or Rh) in 2-propanol for 20 min with 4 molar equiv of L-prolinamide (a 2-fold excess of the ligand to metal was used, as is common practice, although we have determined that smaller ratios, e.g., 2:1, still yield an active catalyst, but with diminished enantioselectivity). This solution was cooled to ambient temperature followed by addition of the desired ketone in 2-propanol. Once this solution had been cooled to the desired temperature (generally −24 °C), the reaction was initiated with the addition of KOH. After 20 h, an aliquot of the catalytic solution was removed via syringe and was evaporated under reduced pressure. This material was subjected to flash chromatography, and the eluate was evaporated under reduced pressure to yield clear oils in each case. ^{1}H NMR spectra of the product alcohols were consistent with previously published results.[4,5]

In the case with (p-CymeneRuCl$_2$)$_2$, catalytic reactions involved a 4.0 mol % loading (Ru:substrate) of **1** for the various substrates, thus producing ee's in the range from 60 to 93% (*R*). Notably, the reduction of 1′-tetralone was found to proceed smoothly and resulted in the highest observed ee although with low conversion (42%) at 20 h. Additionally, 1′-acetonaphthone and acetophenone were reduced with enantiomeric purities of 83% and 79%, respectively. The results are summarized in Table 1.

To further investigate the scope of L-prolinamide as a potential ligand for asymmetric transfer hydrogenations, it was also combined with (Cp*RhCl$_2$)$_2$. Nevertheless, in most cases, these conversions and the enantiomeric purities were inferior to the results with the ruthenium complex.

(1) For examples of asymmetric hydrogenation involving L-proline see: (a) Ohta, T.; Nakahara, S.; Shigemura, Y.; Hattori, K.; Furukawa, I. *Chem. Lett.* **1998**, 491. (b) Tungler, A.; Kajtar, M.; Mathe, T.; Toth, G.; Fogassy, E.; Petro, J. *Catal. Today* **1989**, *5*, 159. (c) Katho, A.; Carmona, D.; Viguri, F.; Remacha, C. D.; Kovacs, J.; Joo, F.; Oro, L. A. *J. Organomet. Chem.* **2000**, *594*, 299. (d) Ohta, T.; Nakahara, S.; Shigemura, Y.; Hattori, K.; Furukawa, I. *Appl. Organomet. Chem.* **2001**, *15*, 699. For examples of hydrogenation with chiral ligands or substrates derived from proline see: (e) Rhyoo, H. Y.; Yoon, Y. A.; Park, H. J.; Chung, Y. K. *Tetrahedron Lett.* **2001**, *42*, 5045 (this paper appeared after the submission of this paper and used substituted amides). (f) Grassert, I.; Schinkowski, K.; Vollhardt, D.; Oehme, G. *Chirality* **1998**, *10*, 754. (g) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173. (h) Munegumi, T.; Maruyama, T.; Takasaki, M.; Harada, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1832. For reviews on transfer hydrogenation see: (i) Zassinovich, G.; Mestroni, G. *Chem. Rev.* **1992**, *92*, 1051. (j) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567. (k) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599.

(2) For selected examples of highly enantioselective and catalytic ketone hydrogenation see: (a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703. (d) Noyori, R.; Ohkuma, T. *Pure Appl. Chem.* **1999**, *71*, 1493. (e) Petra, D. G. I.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Van Loon, A. M.; de Vries, J. G.; Schoemaker, H. E. *Eur. J. Inorg. Chem.* **1999**, 2335. (f) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277. (g) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749.

(3) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993.

(4) Nakamura, K.; Matsuda, T. *J. Org. Chem.* **1998**, *63*, 8957. (See Supporting Information.)

(5) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.

10.1021/om010644v CCC: $20.00
Publication on Web 11/02/2001

Table 1. Asymmetric Hydrogenation Results for Various Ketones with the Catalyst Systems Prepared in Situ from L-Prolinamide and (p-CymeneRuCl$_2$)$_2$, 1, or (Cp*RhCl$_2$)$_2$, 2[a]

cat.	substrate	conv (%)	% ee (config)
1	acetophenone	90	79 (*R*)
1	1′-acetonaphthone	70	83 (*R*)
1	2′-acetonaphthone	74	70 (*R*)
1	1′-tetralone	42	93 (*R*)
1	1′-indanone	65	68 (*R*)
2	acetophenone	66	59 (*R*)
2	1′-acetonaphthone	55	65 (*R*)
2	2′-acetonaphthone	62	35 (*R*)
2	1′-tetralone	39	67 (*R*)
2	1′-indanone	23	70 (*R*)

[a] The substrate to metal ratio was 25:1, and all reactions were carried out at −24 °C for 20 h.

Table 2. Asymmetric Hydrogenation Results for Substituted Acetophenones with the Catalyst System Prepared in Situ from (p-CymeneRuCl$_2$)$_2$ and L-Prolinamide[a]

cat.	substrate	conv (%)	% ee (config)
1	4′-methylacetophenone	64	74 (*R*)
1	4′-methoxyacetophenone	35	73 (*R*)
1	4′-fluoroacetophenone	76	63 (*R*)
1	4′-trifluoromethylacetophenone	94	60 (*R*)

[a] The substrate to metal ratio was 25:1, and all reactions were carried out at −24 °C for 20 h.

The source of the transferred hydrogen atom in similar systems has been attributed to a metal-centered hydride. Perhaps the most widely accepted theory is that a nitrogen atom as well as the metal is intimately involved in the hydride transfer process. Noyori and coworkers[6] have suggested that the transferred hydride originates from an intimate Ru−N−H interaction. These authors have referred to the important Ru−N−H moiety as an example of metal−ligand bifunctional catalysis. This suggests that an N−H moiety might be a prerequisite for an effective catalyst for asymmetric transfer hydrogenation reactions in this system; however, it should be noted that various aprotic sp^2 nitrogen ligands have also been employed.[7]

Although most investigations into enantioselective hydrogenation have focused solely upon the steric factors that are inherent in the substrate, we also examined the possibility that electronic factors were involved. To ensure that the observed results could be attributed to purely electronic effects,[8] substrates involving *para*-substituted acetophenone derivatives were investigated. The results (Table 2) indicated that a strong electron-withdrawing substituent, such as CF_3, was capable of higher conversion but with a lower enantiomeric purity. Conversely, the most electron-donating substituents ($-OCH_3$ and $-CH_3$) led to lower conversion with higher ee. The presence of an electron-withdrawing group has generally been found to facilitate the hydrogen transfer reaction,[9,10] and this has been attributed to the hydridic nature of the reducing species involved. As such, reactions with $-CF_3$ proceeded to higher conversion (and lower ee) owing to rapid hydride transfer, while reactions with electron-donating substituents ($-CH_3$ and $-OCH_3$) proceeded in a slower and more controlled manner, with fluoride being an intermediate case.[11] The unsubstituted derivative, however, does not follow the pattern and proceeded in higher conversion and with higher ee than the substituted derivative. In an analogous reduction of benzaldehyde-d_1 Noyori found a more pronounced effect and observed that the ee of the chiral alcohols increased from 20% for the p-CF_3 derivative to 61% for the p-OCH_3 derivative.[9]

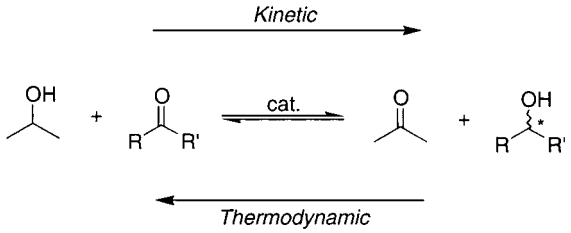

Figure 2. Equilibria between the kinetic and thermodynamic products (R is aryl).

One typical problem with transfer hydrogenation reactions (that exploit alcohols as the sacrificial reductants) is that the initial ee can be degraded as the reaction is allowed to proceed to higher conversion. This occurs because oxidation of benzylic alcohols is thermodynamically favored over reduction relative to the oxidation of aliphatic alcohols.[12] The reversibility of these reactions results in "back-transfer" of hydrogen (from the enantioenriched alcohol) to the generated ketone as depicted in Figure 2. Therefore, we were not surprised to find that a slight decrease in ee occurred at higher conversion with the currently described system. However, the extent of degradation of enantiomeric purity was only found to be ∼5% when the reaction times were extended from 20 to 40 h for the various cases. As such, the reactions were not allowed to reach full conversion, and data were acquired for all cases at 20 h.[13]

A similar catalyst which used proline instead of prolinamide has previously been reported by Furukawa et al.,[1a] in which the catalyst precursor was generated from (p-CymeneRuCl$_2$)$_2$ and L-proline in the presence of 2-propanol. In comparing the Furukawa catalyst with **1**, some of the product ee's were similar, although **1** was found to be superior for certain cases. Notably, while the Furukawa catalyst produced 1′-indanol with an ee of 43% (*R*), **1** produced the respective alcohol with an ee of 68% (*R*). Furthermore, for the reduction of 1′-tetralone, the Furukawa catalyst yielded 8% product (isolated yield, loading Ru:substrate = 1:100 at rt in 24 h) with an increased yield of 37% after heating (5 h at

(6) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 285.
(7) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.
(8) Lowry, H. L.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper Collins: New York, 1987; Chapter 2.
(9) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425.
(10) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.
(11) One measure of the electronic effect is the Hammett σ constant: OMe, −0.268; Me, −0.170; H, 0.000; F +0.062; CF_3, +0.54. McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420.
(12) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.
(13) A potential resolution of the problem of enantioselectivity degradation could be the use of an azeotropic mixture of NEt_3/HCOOH as the sacrificial reductant (an irreversible reaction). This possibility is currently under investigation.

80 °C). However, catalyst **1** (loading Ru:substrate = 1:25) led to a conversion of 42% in 20 h at −24 °C. It should be noted that when acetophenone and 1′-acetonaphthone were reduced with **1** at +25 °C, the reactions reached >70% completion within 10 h. These results suggest a kinetic advantage with catalyst **1**. If the 4:1 mol ratio of L-proline to (*p*-CymeneRuCl$_2$)$_2$ is used as a catalyst under our conditions (−24 °C), there is less than 1% conversion. Since the results differ between the catalysts formed from proline and prolinamide, it would appear that the amide is still intact in the actual catalyst in **1** and was not converted completely to proline. One should also note that proline itself is not very soluble and when in excess may not go into solution. The actual structure of the active catalyst, especially the degree of protonation, however, is not clear. The precatalyst formed from prolinamide and (*p*-CymeneRuCl$_2$)$_2$ appears to be a single isomer of *p*-CymeneRuCl$_2$(prolinamide) characterized in the ^{1}H NMR by diastereotopic isopropyl methyl doublets at δ 1.26 and 1.28 and diastereotopic η^6-arene multiplets at δ 5.23, 5.32, 5.73, and 5.90. Heating of a solution of a mole ratio of dimer to L-prolinamide of 1:4 in chloroform, however, resulted in partial decomplexation of the cymene. Increasing the relative concentration of L-prolinamide resulted in further displacement of cymene, although similar ee's were observed. This would suggest that at least one of the catalytically active species does not contain cymene. For the rhodium case, displacement of the Cp* would not be expected. Regardless, the important species are those that exist under the reaction conditions. The nature of the complexes present under catalytic conditions of heating in alcoholic KOH are unclear, and they will be the subject of further investigation.

In summary, we have discovered a catalytic system that can be readily implemented and leads to secondary alcohols with good to excellent enantioselectivities. The ligands derived from the amides offer an alternative to the amino acids themselves and the potential of improved selectivity. These investigations have also shown that enantiomeric purity of the product can be affected by the electronic factors, as well as steric factors, of the substituents on the substrate. Future investigations will focus upon structural characterization of the catalyst, screening of various other amide-functionalized amino acids, and an extension of substrate compatibility.

Experimental Section

All synthetic manipulations were carried out using standard Schlenk techniques under an inert atmosphere. Reagent grade 2-propanol (Brand-Nu Laboratories) was distilled from CaH_2 and was degassed with freeze−pump−thaw cycles (3 ×) prior to use. Et_2O (Fisher Scientific), L-prolinamide (Aldrich, 98%), and all ketones (Aldrich) were used without further purification. (*p*-CymeneRuCl$_2$)$_2$[14] and (Cp*RhCl$_2$)$_2$ [15] were prepared according to literature procedures. The enantiomeric excess in each product was determined by chiral GC analysis using a Hewlett-Packard 5890A gas chromatograph with a Cyclodex-B chiral column. The absolute configuration of each isolated product was determined by correlation with published specific rotations.[4,6] Optical rotations were measured on a Perkin-Elmer model 341 polarimeter at 589 nm and 25.0 °C, using a 1 dm path length. ^{1}H NMR spectra were recorded on a Bruker 500 MHz or Bruker 400 MHz spectrometer, and chemical shifts are reported in ppm relative to residual solvent peaks (^{1}H).

Catalysis. A typical experimental procedure is described. A flame-dried Schlenk flask was charged with (*p*-CymeneRuCl$_2$)$_2$ (30 mg, 0.049 mmol), excess L-prolinamide (22 mg, 0.19 mmol), and a stir bar. To these components was added 2-propanol (5 mL, dried/degassed), and the resultant solution was heated (100 °C) for 20 min, followed by cooling to ambient temperature. A solution of the desired ketone (2.5 mmol) in 2-propanol (45 mL) was then added to the catalyst mixture, and the solution was cooled to the desired temperature (generally −24 °C). The reaction was initiated with the addition of a solution of KOH (2.5 mL, 0.1 M in 2-propanol). After 20 h, an aliquot of the catalytic solution (1 mL) was removed via syringe and was evaporated under reduced pressure. The resultant oil was subjected to flash chromatography (silica gel-60, Et_2O) and subsequent evaporation under reduced pressure to yield clear liquids in each case. ^{1}H NMR spectral data for the resultant products were consistent with previously reported results.[4,5] (See Supporting Information for details.)

Acknowledgment. We thank the National Science Foundation (Grant CHE0092222) for support of this research.

Supporting Information Available: GC parameters (including retention times). This material is available free of charge via the Internet at http://pubs.acs.org.

OM010644V

(14) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1981**, *21*, 74.
(15) White, C.; Yates, A.; Maitlis, P. M.; Heinekey, D. M. *Inorg. Synth.* **1992**, *29*, 228.