Highly Enantioselective Hydrogenation of Cyclic Enamides Catalyzed by a Rh-PennPhos Catalyst†

Zhaoguo Zhang, Guoxin Zhu, Qiongzhong Jiang, Dengming Xiao, and Xumu Zhang*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received December 17, 1998

Chiral amines are often critical components of pharmaceutical agents. For example, about 15−25% of the single-enantiomer products in development contain this unit according to a recent analysis.[1] The development of practical methods for the synthesis of enantiomerically pure amines is therefore of great interest. Traditional resolution methods and enzymatic transaminase technology are frequent choices in industry for making chiral amines. However, recent attention has been devoted to asymmetric hydrogenation of imines and enamides as potentially more competitive synthetic routes.[2] A variety of transition-metal catalysts have been explored to date for asymmetric hydrogenation of imines, *albeit* with either low enantioselectivity, limited substrate scope, or low activity.[3] Alternatively, asymmetric hydrogenation of simple enamides is a more useful strategy. Several Rh-bisphosphine compounds have been developed as efficient catalysts for asymmetric hydrogenation of acyclic enamides,[4] and some can even tolerate *Z*/*E* mixtures of *β*-substituted enamides as substrates.[4a,c] However, only limited success has been achieved in the hydrogenation of cyclic enamides despite the potential importance of this process for the synthesis of biologically active chiral aminotetralins and aminoindanes.[5] Herein we report the highly enantioselective hydrogenation of cyclic enamides catalyzed by a Rh-PennPhos compound.

In our continuing work on catalytic asymmetric reactions, we have developed conformationally rigid chiral bisphosphines (e.g., BICP = bis(diphenylphosphino)dicyclopentane;[6] phosphinobicyclo[2.2.1]heptanes;[7] PennPhos = *P*,*P*′-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]heptane,[8] Me-PennPhos, Figure 1) and are exploring their synthetic utility. High enantioselectivities have been achieved for the hydrogenation of acyclic enamides with a Rh-BICP catalyst.[4c] However, only modest enantioselectivities (60−70% ee) were obtained for the hydrogenation of cyclic enamides derived from α-tetralone and α-indanone. Encouraged by the excellent results observed upon asymmetric hydrogenation of simple ketones catalyzed by a Rh-PennPhos complex,[8] we have now extended our study of the asymmetric hydrogenation of enamides to include this unique catalytic system.

N-(3,4-Dihydro-1-naphthyl)acetamide was chosen as a typical enamide substrate. This enamide can be easily prepared by reduction of the corresponding oxime with iron powder in the presence of acetic anhydride (Scheme 1).[9a,b] This facile synthesis of enamides[9] combined with an efficient asymmetric hydrogenation step provides a practical protocol for the synthesis of chiral amines from ketones. Table 1 lists asymmetric hydrogenation results under different conditions and with a variety of chiral bisphosphine systems. The catalyst was generally prepared in situ by mixing a solution of a Rh precursor and a phosphine ligand. The reaction was carried out under an initial H_2 pressure of 40 psi at room temperature with a ratio of substrate/Rh/Me-PennPhos of 100:1:1.1. Different Rh catalytic precursors led to large variations in enantioselectivities (entries 1−3). Higher enantioselectivities were observed with cationic Rh precursors (entry 2, 97% ee; entry 3, 98% ee), while the ee is lower with a neutral Rh system (entry 1, 92% ee). Changing solvents and/or H_2 pressure have only a small effect on enantioselectivity, although reaction conversions vary to a large extent. The catalytic hydrogenation goes to completion in methylene chloride, methanol, and 2-propanol under 40 psi of H_2 in 20 h, while only 24% conversion was achieved under the same conditions in toluene. Reactions performed under 15 psi H_2 and 500 psi H_2 in MeOH give similar enantioselectivities (>98% ee) but gave different conversions (6% under 15 psi H_2 and 100% under 500 psi H_2 after 20 h).

Optimal reaction conditions with the Rh-Me-PennPhos catalyst use MeOH as the solvent and an initial H_2 pressure of 40 psi. Under these conditions, we have investigated the Rh-catalyzed asymmetric hydrogenation of *N*-(3,4-dihydro-1-naphthyl)acetamide with several commercially available chiral bisphosphines. Compared with the Rh-Me-PennPhos catalyst, significantly lower enantioselectivities (10% ee, entry 4; 24% ee, entry 5) were observed with Rh-DIOP and Rh-BINAP catalysts. The most surprising result is the low enantioselectivity (1% ee, entry 6) achieved with the Rh-Me-DuPhos complex, which is in sharp contrast to its effective asymmetric hydrogenation of acyclic enamides.[4a] Our results are in agreement with the investigation by Burk,[9b] who found that under similar conditions hydrogenation of *N*-(3,4-dihydro-1-naphthyl)acetamide gave 0% ee with a Rh-Me-DuPhos complex and 69% ee with a Rh-Me-BPE catalyst. However, up to 92% ee was reported with a Rh-Me-BPE catalyst if the reaction was done at 0 °C.[9b] To the best of our knowledge, Rh-Me-PennPhos-catalyzed asymmetric hydrogenation of *N*-(3,4-dihydro-1-naphthyl)acetamide gives the highest enantioselectivity reported to date.

† Dedicated to Professor Xiyan Lu on the occasion of his 70th birthday.

(1) Cannarsa, M. S. *Proceedings of the Chiral USA'97 Symposium*; Matrix, 1997; and a related report of *Technol. Catal. Int.*

(2) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(3) (a) Spinder, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558. (b) Chan, Y. Ng C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (c) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G. J.; Rettig, S. J. *Inorg. Chem.* **1991**, *30*, 5002. (d) Lensink, C.; Vries, J. G. *Tetrahedron: Asymmetry* **1992**, *3*, 235. (e) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562. (f) Willoughby, C. A.; Buchwald, S. L *J. Am. Chem. Soc.* **1994**, *116*, 8952. (g) Chan, A. S. C.; Chen, C. C.; Lin, C. W..; Lin, Y. C.; Cheng, M. C. *J. Chem. Soc., Chem. Coummn.* **1995**, 1767. (h) Verdaguer, X.; Jange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784. (i) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 14575. (j) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (k) Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M.; Kruger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887.

(4) For recent advances, see: (a) Burk, M. J.; Wang, Y. M.; Lee, R. J. *J. Am. Chem. Soc.* **1996**, *118*, 5142. (b) Zhang, F.-Y.; Pai, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808. (c) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590.

(5) One example was reported on asymmetric hydrogenation of *N*-(6-bromo-1,2,3,4-tetrahydronaphthalene)yl benzamide using a Ru-BINAP catalyst: Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324.

(6) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799.

(7) (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (b) Chen, Z.; Jiang, Q.; Zhu, G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 4521.

(8) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1100.

(9) (a) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100. (b) Burk, M. J.; Casey, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. For the origin of this Fe/Ac_2O method, see: (c) Boar, R. B.; McGhie, J. F.; Robonson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237. (d) Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605.

10.1021/jo9824605 CCC: $18.00
Published on Web 02/27/1999

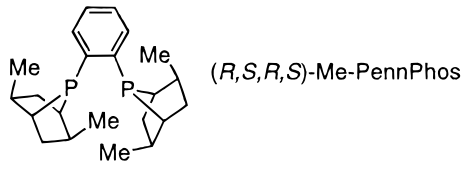


Figure 1.

Scheme 1

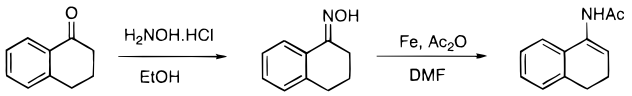
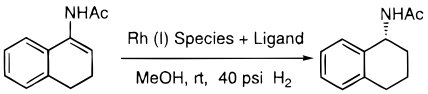


Table 1. Rh-Catalyzed Asymmetric Hydrogenation of an Enamide[a]



entry	Rh(I) species	ligand	% ee[b]
1	$[Rh(COD)Cl]_2$	(*R*,*S*,*R*,*S*)-Me-PennPhos	92 (*R*)
2	$Rh(COD)_2BF_4$	(*R*,*S*,*R*,*S*)-Me-PennPhos	97 (*R*)
3	$Rh(COD)_2PF_6$	(*R*,*S*,*R*,*S*)-Me-PennPhos	98 (*R*)
4	$Rh(COD)_2PF_6$	(+)-DIOP	10 (*S*)
5	$Rh(COD)_2PF_6$	(*R*)-BINAP	24 (*R*)
6	$Rh(COD)_2PF_6$	(*R*,*R*)-Me-DuPhos	1[c] (*R*)

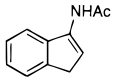
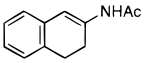
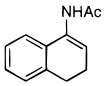
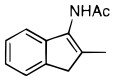
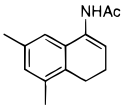
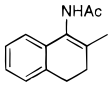
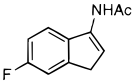
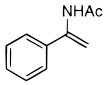
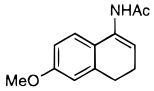
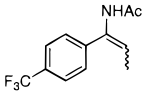
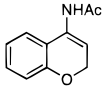
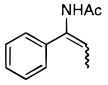
[a] The reaction was complete in quantitative yield at room temperature under an initial hydrogen pressure of 40 psi after 20 h using MeOH as the solvent. The catalyst was made in situ by stirring a solution of Rh precursor and phosphine ligand in MeOH for 30 min [[substrate (0.5 mmol, 0.17 M)/Rh cat./ligand = 1:0.01:0.011]]. [b] Enantiomeric excesses were determined by chiral GC using a Supelco chiral Select 1000 (0.25 mm × 15 m) column. [c] 57% conversion.

To demonstrate that this is a potentially practical method for the synthesis of α*-aminotetralins, we increased the ratio of N-(3,4-dihydronaphthalen-1-yl)acetamide/Rh-Me-PennPhos to 2000:1 and the reaction was still complete in 20 h with 98% ee.*

Using these optimal conditions, several cyclic and acyclic enamides were investigated (Table 2). Hydrogenation of several cyclic enamides derived from α-tetralones and α-indanones (entries 1−5) gives high enantioselectivities (>97% ee) regardless of the substituents on the aromatic ring.[10] Interestingly, a tetrasubstituted five-membered cyclic enamide gives high enantioselectivity (98% ee, entry 8). However, the ee with the corresponding six-membered cyclic enamide (73% ee, entry 9) is significantly lower. Only moderate ee was observed for the enamide made from *β*-tetralone (entry 7). Burk et al. reported excellent results (>98% ee) for the asymmetric hydrogenation of an indanone-derivated enamide using a Rh-Me-DuPhos catalyst.[9b] The profile of their catalytic systems has not yet been completely established for a variety of cyclic enamides. Using the Rh-Me-PennPhos catalyst, several acyclic enamides were hydrogenated with moderate to good ee's (entries 10−12).

(10) The absolute configuration was determined by comparing the GC trace and optical rotation of the acetamide derived from (*R*)-α-aminoindane and (*R*)-α-aminotetralin purchased from Lancaster, Inc.

Table 2. Asymmetric Hydrogenation of Enamides Catalyzed by a Me-PennPhos-Rh Complex

Entry	Substrate	% ee[b]	Entry	Substrate	% ee[b]
1		98	7		71
2		98	8		98
3		>99	9		73
4		>99	10		75
5		97	11		88
6		90	12		90

[a] The reaction was complete in quantitative yield at room temperature under an initial hydrogen pressure of 40 psi after 20 h using MeOH as the solvent. The catalyst was made in situ by stirring a solution of $[Rh(COD)_2]PF_6$ and Me-PennPhos in MeOH for 30 min [[substrate (0.5 mmol, 0.17 M)/$[Rh(COD)_2]PF_6$/ligand = 1:0.01:0.011]]. [b] Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm × 15 m) column.

However, these enantioselectivities are lower than those obtained with Rh-DuPhos, Rh-BICP, and other catalytic systems.[4] Since there is as yet no universal catalyst to handle such a diverse set of substrates, the Rh-PennPhos complex serves to compliment other efficient catalysts[4] for hydrogenation of simple acyclic enamides.

In summary, we have developed a highly enantioselective Rh-PennPhos catalyst for asymmetric hydrogenation of cyclic enamides. The high reactivity and ease of operation combined with an efficient method for the synthesis of substrates make this reaction an attractive synthetic procedure for the synthesis of enantiomerically pure α-aminotetralins and α-aminoindanes.

Acknowledgment. This work was supported by a Camille and Henry Dreyfus New Faculty Award and Teacher Scholar Award, an ONR Young Investigator Award, a DuPont Young Faculty Award, Catalytica Pharmaceuticals, and DuPont Agricultural Products. We acknowledge a generous loan of precious metals from Johnson Matthey, Inc. and a gift of chiral GC columns from Supelco and thank Dr. Albert L. Casalnuovo of DuPont Agricultural Products for useful suggestions for enamide synthesis.

Supporting Information Available: Spectroscopic data and experimental details.

JO9824605