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Rh-catalyzed asymmetric hydrogenation by using a new family of C_2-symmetric bisphosphinites and a bisaminophosphine as ligands

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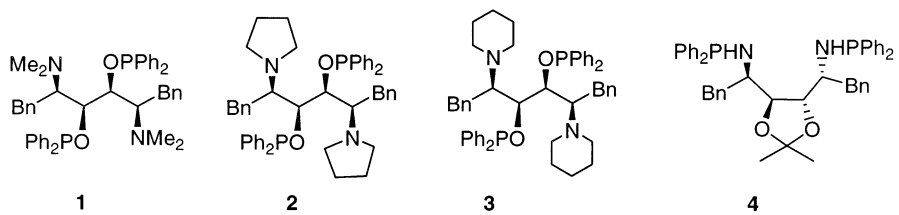
Abstract—The application of a new family of four-chiral-centered C_2-symmetric bisphosphinites (**1**, **2** and **3**) and the bisaminophosphine **4** in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids has been examined. Up to 98% ee was obtained in the hydrogenation of α-acetamidocinnamic acid, which is comparable with the enantioselection obtained from the best chiral bisphosphinites and bisaminophosphines.

Transition metal-catalyzed asymmetric synthesis and reactions have been recognized as the most fruitful and efficient methods for preparing optically active substances.[1] To achieve high stereoselection, it is crucial to design and prepare efficient chiral ligands. Up to now, a large number of monodentate, C_2-symmetric or pseudo C_2-symmetric bidentate and multidentate ligands have been widely reported in a variety of catalytic asymmetric reactions.[1–3] Amongst these, optically active diphosphine ligands (e.g. BINAP, DIOP, BDPP, DUPHOS, CHIRAPHOS and BICP) with C_2-symmetry have been well documented as being able to create effective chiral environments for substrates and nucleophiles,[4] and they have been widely employed in a large number of transition metal-catalyzed reactions, especially in the rhodium-catalyzed asymmetric hydrogenation of prochiral dehydroprecursors.[1,5] In fact, asymmetric hydrogenation is one of the most practical methods in asymmetric synthesis, accounting for 70% of all procedures used on a commercial scale,[6] and it has become a prototype for evaluation of new chiral diphosphine catalysts. In contrast to many chiral diphosphines reported in the literature, chiral phosphinites employed in transition metal-catalyzed asymmetric reactions are generally recognized as poor ligands with few exceptions,[7] due to their lower electron donating ability and increased conformational flexibility relative to phosphines. In recent years, Selke[8] and RajanBabu[8d] have reported the use of a series of chiral phosphinite ligands derived from natural chiral pools (e.g. carbohydrates and tartaric acids) to give good to excellent results in rhodium-catalyzed asymmetric hydrogenation. Zhang[9] and Chan[10] also reported that rhodium complexes bearing (*R*)- or (*S*)-spiro phosphinite ligands are highly effective in the enantioselective hydrogenation of dehydroamino acids and their esters. Very recently, bisaminophosphines were also found to be effective ligands for catalytic hydrogenation reactions leading to chiral amino acids, but only a limited number of bisaminophosphines have been investigated.[11]



1 **2** **3** **4**

Scheme 1.

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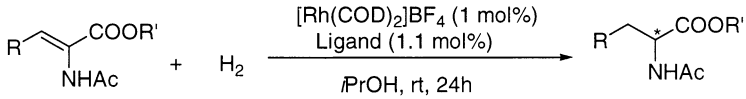
Table 1. Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives[a]



Entry	Ligand	Substrate	Yield (%)	Ee (%)[b]
1	**1**	R = H, R′ = Me	72	41
2	**2**	R = H, R′ = Me	77	46
3	**3**	R = H, R′ = Me	80	48
4	**4**	R = H, R′ = Me	77	68
5	**1**	R = Ph, R′ = H	98	94[c]
6	**2**	R = Ph, R′ = H	94	89[c]
7	**3**	R = Ph, R′ = H	98	97[c]
8	**4**	R = Ph, R′ = H	99	98[c]
9	**1**	R = 4-MeOPh, R′ = Me	97	90
10	**4**	R = 4-MeOPh, R′ = Me	99	91

[a] The reactions were performed at room temperature under 1 atm of H_2 for 24 h: [substrate/$[Rh(COD)_2]BF_4$/ligand = 1:0.01:0.011].
[b] Determined by HPLC using Chiralcel AD or OJ columns.
[c] The ee value was determined after converting the products to the corresponding methyl ester.

In the course of our studies in the field of asymmetric synthesis and reactions, we have developed a new family of C_2-symmetric bisphosphinites **1**, **2** and **3** and bisaminophosphine **4**, which have proven to be good ligands in asymmetric allylic substitution.[12] To probe further the potential of this family in asymmetric reactions, we have investigated their efficiency in asymmetric hydrogenation. Here are the preliminary results (Scheme 1).

First, we chose the often employed substrate, methyl α-acetamidoacrylate, as the model. The asymmetric hydrogenation was performed at ambient temperature with 1 atm of hydrogen in the presence of the Rh catalyst, which was formed in situ by mixing $[Rh(COD)_2]BF_4$ with 1.1 mol. equiv. of the ligand under an inert atmosphere. Entries 1–4 in Table 1 summarize the results of asymmetric hydrogenation employing our new ligands. The reaction was carried out in propan-2-ol with good yields and moderate stereoselection (41–48% ee) when phosphinites **1**–**3** were used as the ligand, whilst up to 68% ee was obtained in the case of bisaminophosphine **4**.

We then tested the stereoselection by using α-acetamidocinnamic acid as the hydrogenation substrate. Under the same conditions we found that the C_2-symmetric bisphosphinites **1** and **3** gave ees of 94 and 97%, respectively (entries 5 and 7), and the bisphosphinite **2** gave a slightly lower ee of 89% (entry 6). The highest enantioselectivity of 98% (entry 8) was obtained by using bisaminophosphine **4** as the ligand.

Finally, we chose an α-acetamidocinnamic ester with a methoxy substituent in the 4-position of the phenyl ring as the substrate. Up to a 90% ee was achieved with phosphinite **1** and bisaminophosphine **4** as the ligands (entries 9–10).

Unlike the results obtained using other bisphosphine ligands, the prochiral dehydroamino acid or ester substrates significantly affected the catalytic activity and enantioselectivity in our system. There are four stereogenic carbon centers in our ligand system and the absolute configuration of the four stereogenic carbon centers dictate the orientation of the four *P*-phenyl groups similar to Zhang and Chan's results.[9,10,13] For the bisphosphinites **1**, **2** and **3**, a seven-membered ligand–Rh complex was formed, while a nine-membered ligand–Rh complex was the product from bisaminophosphine **4**. The high enantioselectivities for the two kinds of ligand–Rh complexes in the hydrogenation of α-acetamidocinnamic acid suggest a rational matching of the catalyst chiral environment with the substrate. The low enantioselectivity in the hydrogenation of methyl α-acetamidoacrylate was attributed to less bulky substituents in the substrate compared to the α-acetamidocinnamic acid. Further exploitation of the relationship between the catalyst and substrate are ongoing.

In summary, the application of the new family of four-chiral-centered C_2-symmetric bisphosphinites **1**, **2** and **3** and the bisaminophosphine **4** in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids has been studied. Up to a 98% ee was obtained in the hydrogenation of α-acetamidocinnamic acid, while only moderate enantioselectivity was observed in the case of methyl α-acetamidoacrylate. Our results for the asymmetric hydrogenation of acetamidocinnamic acid are comparable with the enantioselection obtained from the best chiral bisphosphinites and bisaminophosphines.

References

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993.
2. Sheldon, R. A. *Chirotechnology*; Marcel Dekker: New York, 1993.

3. (a) Kotha, S. *Tetrahedron* **1994**, *50*, 3639; (b) Brunner, H. In *Topics in Stereochemistry*; Interscience: New York, 1988; Vol. 18, p. 129; (c) *Handbook of Enantioselective Catalysis*; Brunner, H.; Zettlmeier, W., Eds.; VCH: New York, 1993; Vol. 2.
4. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
5. (a) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106; (b) Noyori, R. *Science* **1990**, *248*, 1194; (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345; (d) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901; (e) Benincori, T.; Brenna, E.; Sannicolo, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244; (f) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510.
6. Cannarsa, M. S. Proceeding of the Chiral USA'97 Symposium; Matrix, 1997; and a related report of Technol. Catal. Int.
7. (a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101; (b) Seebach, D.; Devaquet, E.; Ernst, A.; Hayakawa, M.; Kuhnle, F. N. M.; Schweizer, W. B.; Weber, B. *Helv. Chim. Acta* **1995**, *78*, 1636; (c) Roucoux, A.; Thieffry, L.; Carpentier, J.-F.; Devocelle, M.; Meliet, C.; Agbossou, F.; Mortreux, A. *Organometallics* **1996**, *15*, 2440; (d) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570; (e) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012.
8. (a) Selke, R.; Pracejus, H. *J. Mol. Catal.* **1986**, *37*, 213; (b) Selke, R. *J. Mol. Catal.* **1986**, *37*, 227; (c) Selke, R.; Schwartze, M.; Baudisch, H.; Grassert, I.; Michalik, M.; Oehme, G.; Stoll, N.; Costisella, B. *J. Mol. Catal.* **1993**, *84*, 223; (d) Kumar, A.; Oehme, G.; Roque, J. P.; Schwartze, M.; Selke, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2197.
9. Zhu, G. X.; Zhang, X. M. *J. Org. Chem.* **1998**, *63*, 3133.
10. Chen, Y.; Li, X.; Tong, S.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 957.
11. (a) Zhang, F. Y.; Pai, C. C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808; (b) Yan, M.; Yang, L. W.; Hu, W. H.; Zhang, F. Y.; Chan, A. S. C. *Bull. Inst. Chem., Academia Sinica* **1999**, *46*, 19.
12. Zhang, A.; Feng, Y.; Jiang, B. *Tetrahedron: Asymmetry* **2000**, *11*, 3123.
13. Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799.