J|A|C|S
COMMUNICATIONS

Published on Web 08/19/2006

Highly Efficient Rh(I)-Catalyzed Asymmetric Hydrogenation of Enamines Using Monodente Spiro Phosphonite Ligands

Guo-Hua Hou, Jian-Hua Xie, Li-Xin Wang, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Received June 23, 2006; E-mail: qlzhou@nankai.edu.cn

Chiral amines are an important class of compounds in organic and pharmaceutical synthesis, and a great effort has been made to develop efficient synthetic methods for chiral amines. In the past decades, the catalytic asymmetric hydrogenation of functionalized enamines, such as α- and *β*-*N*-acylamino acrylates, and enamides have been extensively studied, and a great number of highly enantioselective protocols for the synthesis of enantiomer-enriched primary and secondary amines have been documented.[1] However, only a limited progress has been achieved in the direct preparation of chiral tertiary amines, which broadly occurred in the biologically active molecules and natural products,[2] by asymmetric hydrogenation of the corresponding *N*,*N*-dialkylenamines. This is not surprising because one substantial drawback in the current approaches to asymmetric hydrogenation of enamides is the requirement of an *N*-acyl group in the substrate.[3] This *N*-acyl group is considered indispensable for the substrate to form a chelate complex with metal of catalyst in transition state, giving a good reactivity and enantioselectivity. Up to now, only two groups have tackled the challenging class of *N*,*N*-dialkylenamine substrates in the asymmetric hydrogenation.[4] In 1994, Buchwald et al.[5] reported the first example of catalytic asymmetric hydrogenation of simple enamines. By using 5 mol % chiral titanocene catalyst [(*S*,*S*,*S*)-(EBTHI)TiO_2-binaphtho] they achieved excellent enantioselectivities (up to 98% ee) in the hydrogenation of 1-(dialkylamino)-1-arylethenes. Few years later, Börner and co-workers[6] used chiral Rh(I)-diphosphine complexes for this hydrogenation and obtained the chiral tertiary amines in moderate enantiomeric excesses (up to 72%). These results are very encouraging and suggested that new efficient catalysts are necessary for the development of highly enantioselective hydrogenation of simple nonfunctionalized enamines to give chiral tertiary amines in broad scope.

Recently, we demonstrated that the chiral monodentate phosphoramidites and phosphonites containing a 1,1′-spirobiindane scaffold were highly enantioselective ligands for the Rh-catalyzed asymmetric hydrogenation of *N*-(α-arylethenyl)-acetamides and *N*-acyl α- and *β*-dehydroamino acid derivatives.[7] As a part of our sustained efforts in this area, we herein wish to report the asymmetric hydrogenation of *N*,*N*-dialkylenamines using chiral spiro phosphonite ligands **1**, providing chiral tertiary amines in excellent enantiomeric excesses (up to 99.9%).

The chiral tertiary 1,2-diarylethanamine is a very useful unit; it widely exists in natural products such as benzylisoquinolines.[8] The catalytic asymmetric hydrogenation of *N*,*N*-dialkylenamines is one of the most straightforward accesses to the optically active tertiary 1,2-diarylethanamines. In our study, the hydrogenation of (*E*)-1-(1-pyrrolidinyl)-1,2-diphenylethene (**2a**) was initially performed under 100 atm of H_2 in THF with the rhodium catalyst generated in situ from 1 mol % $[Rh(COD)_2]BF_4$ and 2.2 mol % phosphorus ligands. A brief screening on the chiral phosphorus ligands available in our laboratory showed that the diphosphine ligands including BINAP, SDP, and JosiPhos were inefficient in the reaction (ee ≤ 10%). Most of monophosphorus ligands illustrated in Scheme 1 also gave very low enantioselectivity (ee ≤ 14%) except for spiro phosphonite ligand (*S*)-**1c**, which provided chiral tertiary amine **3a** in 33% ee (Table 1, entry 3).

Scheme 1

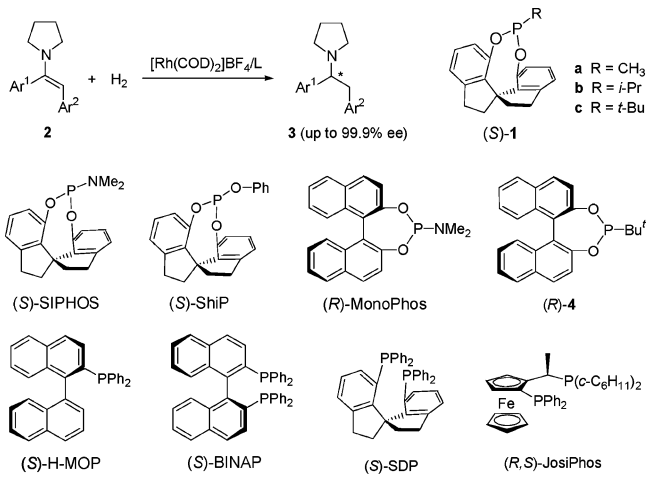

Table 1. Rh(I)-Catalyzed Asymmetric Hydrogenation of Enamine **2a**, Optimizing Reaction Conditions[a]

entry	ligand	solvent	PH_2 (atm)	time (h)	addition (mol %)	ee (%)[b]
1	(*S*)-**1a**	THF	100	48	none	14
2	(*S*)-**1b**	THF	100	48	none	4
3	(*S*)-**1c**	THF	100	48	none	33
4	(*S*)-**1c**	THF	100	48	I_2 (5)	71
5	(*S*)-**1c**	THF	100	48	I_2 (2)	83
6	(*S*)-**1c**	THF	100	48	I_2 (1)	77
7	(*S*)-**1c**	Et_2O	100	48	I_2 (2)	66
8	(*S*)-**1c**	dioxane	100	48	I_2 (2)	72
9	(*S*)-**1c**	CH_2Cl_2	100	48	I_2 (2)	78
10	(*S*)-**1c**	toluene	100	48	I_2 (2)	60
11	(*S*)-**1c**	DME	100	48	I_2 (2)	20
12	(*S*)-**1c**	MeOH	100	48	I_2 (2)	12
13	(*S*)-**1c**	THF	100	12	I_2/HOAc (2/50)	78
14	(*S*)-**1c**	THF	30	12	I_2/HOAc (2/30)	78
15	(*S*)-**1c**	THF	10	12	I_2/HOAc (2/20)	87
16[c]	(*S*)-**1c**	THF	10	24	I_2/HOAc (2/20)	77
17	(*S*)-**1c**	THF	5	22	I_2/HOAc (2/20)	80
18	(*S*)-**1a**	THF	10	12	I_2/HOAc (2/20)	32
19	(*S*)-**1b**	THF	10	12	I_2/HOAc (2/20)	62
20	(*R*)-**4**	THF	10	12	I_2/HOAc (2/20)	56
21	(*S*)-ShiP	THF	10	12	I_2/HOAc (2/20)	33

[a] Reaction conditions: 1 mol % $[Rh(COD)_2]BF_4$, 2.2 mol % ligand, [substrate] = 0.125 M, room temperature, 100% conversion. [b] Determined by chiral HPLC using a chiralcel OD-H column. [c] With 0.5 mol % catalyst, 87% conversion.

It was reported that the additives might play a crucial role for the high reactivity and enantioselectivity in the hydrogenations of simple olefins,[9] ketones,[10] and imines.[11] To improve the enantio-

10.1021/ja0644778 CCC: $33.50

selectivity in the hydrogenation of enamine **2a** catalyzed by Rh/(*S*)-**1c** complex, we investigated the effect of additives. When *o*-phthalimide, HOAc, or H_2SO_4 were added, the catalyst was strongly deactivated and only very low conversions were obtained. However, a promising result was obtained when I_2 was added. In the presence of 5 mol % I_2, the enantioselectivity of reaction was dramatically increased to 71% ee (entry 4). Adjusting the amount of I_2, we found that 2 mol % I_2 was suitable for achieving a high enantioselectivity (83% ee) (entry 5). Different solvents were then compared in the presence of 2 mol % I_2. A full conversion was obtained in all tested solvents. In addition to THF, the solvents including Et_2O, dioxane, CH_2Cl_2, and toluene also could be employed, albeit the enantioselectivities were slightly lower (60−78% ee). However, the reactions in MeOH and chelate solvent DME (1,2-dimethoxyethane) had very low enantioselectivities (entries 11 and 12). Although the addition of I_2 significantly improved the enantioselectivity of hydrogenation of enamine **2a**, the reaction rate was still too low.

Acid was often utilized to accelerate the reaction rate in the Ir(I)-catalyzed asymmetric hydrogenation of imines by preventing deactivation of the catalyst caused by the amine products.[12] It was mentioned above that the use of acetic acid alone in this Rh(I)-catalyzed hydrogenation of enamines strongly lowered the conversion. Surprisingly, when the acetic acid was used together with 2 mol % of I_2 in the hydrogenation of enamine **2a**, the reaction rate was remarkably increased. In the presence of 20−50 mol % of acetic acid the reaction time was shortened from 48 to 12 h without losing enantioselectivity. A more significant improvement brought about by the addition of I_2 and acetic acid was that the hydrogenation could proceed under a much lower pressure of H_2, which was beneficial to high enantioselectivity. For example, employing 2 mol % I_2 and 20 mol % acetic acid as additives, the hydrogenation of **2a** was completed in 12 h under 10 atm of hydrogen, affording the amine **3a** in 87% ee (entry 15). The comparison of ligands **1** under the optimized conditions showed that the enantioselectivity of catalyst was constantly enhanced as the size of R group in the ligands **1** became larger. The ligand **1c**, which contained a *tert*-butyl gave the best result. Other ligands listed in Scheme 1 were also evaluated in combination with iodine/acetic acid. Most of them showed no enantioselectivity, with ligands **4** (56% ee) and ShiP (33% ee) being exceptions.

A variety of (*E*)-1-(1-pyrrolidinyl)-1,2-diarylethenes **2** can be successfully hydrogenated using $[Rh(COD)_2]BF_4$/(*S*)-**1c** catalyst to produce the corresponding tertiary amines **3** in good to excellent ee values (Table 2). The electronic nature of the aryl groups of enamines **2** had a strong influence on the enantioselectivity of the reaction. The substrates with a Ar^1 connecting electron-donating groups such as Me or MeO have higher enantioselectivity (entries 2−6). However, on the Ar^2 side, a reverse effect was observed. The substrates with a Ar^2 connecting electron-withdrawing groups such as Cl, Br, and F on para-position gave higher enantioselectivity. The highest enantioselectivity (99.9% ee) was achieved in the hydrogenation of enamine **2n**, which has a 4-F on Ar^2 (entry 14). The effect of *N*-alkyl groups of enamine substrates on the enantioselectivity of reaction was also examined. When the pyrrolidine moiety was changed to piperidine and morpholine the ee values of hydrogenation products were lowered to 75% and 77%, respectively.

In summary, a highly enantioselective hydrogenation of simple *N*-unprotected enamines catalyzed by a Rh(I) complex of chiral spiro phosphonite ligand (*S*)-**1c** has been developed, which provided a straightforward method for the synthesis of chiral tertiary amines with excellent ee values. Further investigation will focus on the reaction mechanism and the extension of this novel catalytic system to a broader rang of enamines.

Table 2. The Asymmetric Hydrogenation of Enamines **2** Catalyzed by Rh(I)/(*S*)-**1c** Complex[a]

entry	Ar^1	Ar^2	product	ee (%)[b]
1	C_6H_5 (**2a**)	C_6H_5	**3a**	87
2	4-MeC_6H_4 (**2b**)	C_6H_5	**3b**	91
3	3-MeC_6H_4 (**2c**)	C_6H_5	**3c**	90
4	2-MeC_6H_4 (**2d**)	C_6H_5	**3d**	90
5	4-$MeOC_6H_4$ (**2e**)	C_6H_5	**3e**	95
6	3,4-$(MeO)_2C_6H_3$ (**2f**)	C_6H_5	**3f**	99
7	4-ClC_6H_4 (**2g**)	C_6H_5	**3g**	73
8	C_6H_5 (**2h**)	2-MeC_6H_4	**3h**	94
9	C_6H_5 (**2i**)	2-ClC_6H_4	**3i**	93
10	C_6H_5 (**2j**)	3-ClC_6H_4	**3j**	90
11	C_6H_5 (**2k**)	4-MeC_6H_4	**3k**	80
12	C_6H_5 (**2l**)	4-ClC_6H_4	**3l**	96
13	C_6H_5 (**2m**)	4-BrC_6H_4	**3m**	97(*R*)[c]
14	C_6H_5 (**2n**)	4-FC_6H_4	**3n**	99.9
15	3-MeC_6H_4 (**2o**)	4-FC_6H_4	**3o**	90
16	4-$MeOC_6H_4$ (**2p**)	4-FC_6H_4	**3p**	95
17	4-$MeOC_6H_4$ (**2q**)	4-ClC_6H_4	**3q**	93

[a] $[Rh(COD)_2]BF_4$/(*S*)-**1c**/I_2/HOAc/substrate = 1:2.2:2:20:100, [substrate] = 0.125 M, THF, rt, 10 atm H_2, 12 h, 100% conversion. [b] Determined by HPLC using chiral columns (see Supporting Information). [c] Determined by X-ray diffraction analysis (see Supporting Information).

Acknowledgment. We thank the National Natural Science Foundation of China, and the Ministry of Education of China for financial support.

Supporting Information Available: Experimental procedures, the characterizations of substrates and products, the analysis of ee values of hydrogenation products (PDF), and the crystal data and structure refinement for (*R*)-**3m**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review, see: Tang, W.-J.; Zhang, X.-M. *Chem. Rev.* **2003**, *103*, 3029.
(2) (a) Keay, J. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8. (b) *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier: Oxford, 1999; Vols. 1−9.
(3) For a review, see: Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; p 41.
(4) For the examples of asymmetric hydrogenation of *N*-unprotected *β*-aminoesters and amides, see: (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918. (b) Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343.
(5) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985.
(6) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2000**, *41*, 2351.
(7) (a) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, 480. (b) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348. (c) Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2004**, *69*, 8157.
(8) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, The Netherlands, 1998; p 255.
(9) (a) Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, *502*, 169. (b) Buriak, J. M.; Klein, J. C.; Herrington, D. G.; Osborn, J. A. *Chem. Eur. J.* **2000**, *6*, 139.
(10) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100.
(11) (a) Spindler, F.; Pugin, B.; Jalett, H.-P.; Buser, H.-P.; Pittelkow, U.; Blaser, H.-U. *Chem. Ind. (Dekker)* **1996**, *68*, 153. (b) Spindler, F.; Blaser, H.-U.; *Enantiomer* **1999**, *4*, 557. (c) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (d) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536.
(12) Blaser, H. U.; Buser, H. P.; Coers, K.; Hanreich, R.; Jalett, H. P.; Jelsch, E.; Pugin, B.; Schneider, H. D.; Spindler, F.; Wegmann, A. *Chimia* **1999**, *53*, 275.

JA0644778