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ENANTIOSELECTIVE HYDROGENATION OF 3,4-DIHYDRO-β-CARBOLINES CATALYZED BY Ir COMPLEXES OF DIPHOSPHINE

Toshiaki Morimoto,* Naoaki Suzuki, and Kazuo Achiwa

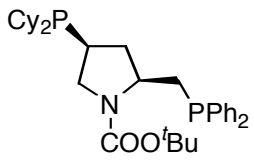
School of Pharmaceutical Sciences, University of Shizuoka,
52-1 Yada, Shizuoka-shi 422-8526, Japan
*e-mail: morimtt@u-shizuoka-ken.ac.jp

Abstract – A catalytic system, Ir(I)-BINAP-tetrafluorophthalimide, was found to be very efficient in the asymmetric hydrogenation of 3,4-dihydro-1-methyl-β-carbolines, showing high enantioselectivity of 95% ee.

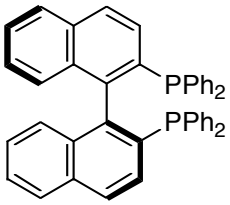
Optically active amines are important components of physiologically active compounds such as alkaloids and medicines. Among the alkaloids, a series of chiral tetrahydroisoquinolines is one of the most important categories.[1] Numerous methods for the preparation of such compounds have been reported;[2] however, most of the methods are based on the procedures using a stoichiometric amount of chiral building blocks, auxiliaries, or reagents. Recently, several efficient methods employing chiral catalysts have been developed such as asymmetric hydrogenations using a Ru-BINAP catalyst,[3] a chiral titanocene catalyst,[4] an Ir-BCPM (or BINAP) catalyst,[5] and a Ru-*N*-monosulfonated diamine catalyst.[6] We previously reported modified asymmetric hydrogenations of cyclic imines with our original diphosphine ligands, BCPM and MOD-DIOP, Ir(I) catalyst, and additives such as tetrabutylammonium iodide, bismuth(III) iodide, and phthalimides.[5,7] Among the additives, phthalimides and other five-member imides were found to be highly effective in improving the enantioselectivity and the catalytic activity of an Ir(I) complex of BCPM. In our effort to expand the scope of this excellent methodology, we explored the asymmetric hydrogenation of other cyclic imine substrates for obtaining optically active tetrahydroharmans. Herein we wish to report the asymmetric hydrogenation of 3,4-dihydro-1-methyl-β-carbolines using the catalyst system for the synthesis of (1*S*)-1,2,3,4-tetrahydroharman and (1*S*)-1,2,3,4-tetrahydroharmine.

First, asymmetric hydrogenation of 3,4-dihydroharman (3,4-dihydro-1-methyl-β-carboline) (**1**) was carried out under 100 atm H_2 with 1 mol% of a catalyst complex prepared *in situ* from $[Ir(cod)Cl]_2$ and (2*S*,4*S*)-BCPM in the presence of an additive (Bu_4N•I, BiI_3, or phthalimide) (molar ratio: **1**/Ir/ligand/additive=100/1/1.2/2) in a mixed solvent of benzene (or toluene) and methanol (Entries 1-3 in Table 1). Although the hydrogenation proceeded in good conversion yield, the enantioselectivity of all the products was disappointingly low (<30% ee). Therefore, we next employed (*S*)-BINAP as a ligand.

Ligand:

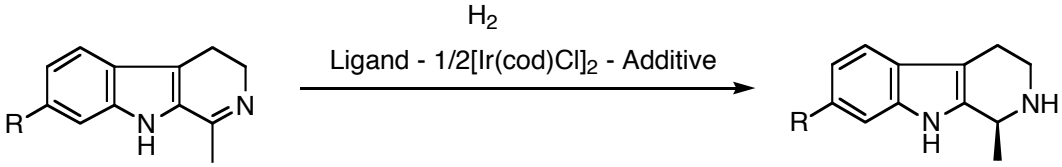


(2*S*,4*S*)-BCPM



(*S*)-BINAP

Table 1. Asymmetric Hydrogenation of 3,4-Dihydro-1-methyl-β-carbolines Catalyzed by an Ir-Diphosphine Complex[a]



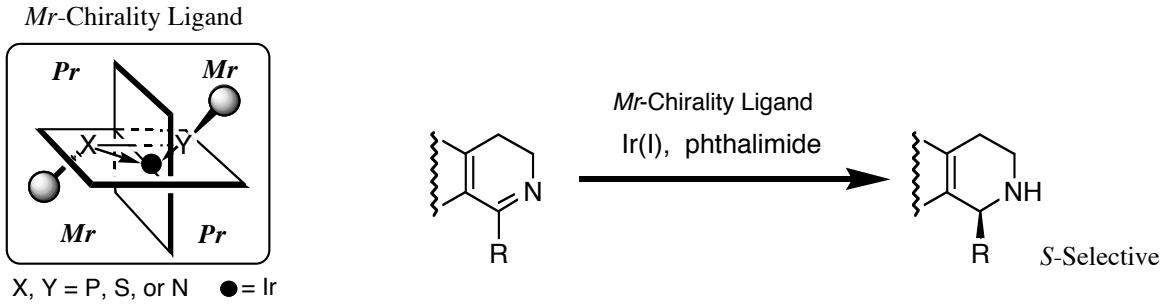
1, 3 **1, 2**: R=H; **3, 4**: R=MeO **2, 4**

Entry	Substrate	Ligand	Additive	Solvent	Temp. (°C)	Time (h)	Conv.[b] (%)	Ee[c] (%)
1	**1**	(2*S*,4*S*)-BCPM	$Bu_4N•I$	benzene-MeOH	20	90	81	22 (*R*)
2	**1**	(2*S*,4*S*)-BCPM	BiI_3	benzene-MeOH	20	48	97	30 (*R*)
3	**1**	(2*S*,4*S*)-BCPM	phthalimide	toluene-MeOH	5	40	71	20 (*S*)
4	**1**	(*S*)-BINAP	none	toluene-MeOH	5	40	92	10 (*S*)
5	**1**	(*S*)-BINAP	phthalimide	mesitylene-CH_2Cl_2-MeOH	5	40	40	70 (*S*)
6	**1**	(*S*)-BINAP	F_4-phthalimide	mesitylene-CH_2Cl_2-MeOH	5	40	55	**82** (*S*)
7	**3**	(2*S*,4*S*)-BCPM	F_4-phthalimide	mesitylene-CH_2Cl_2-MeOH	5	20	99	41 (*S*)
8	**3**	(*S*)-BINAP	none	mesitylene-CH_2Cl_2-MeOH	5	20	32	62 (*S*)
9	**3**	(*S*)-BINAP	phthalimide	mesitylene-CH_2Cl_2-MeOH	5	40	65	72 (*S*)
10	**3**	(*S*)-BINAP	F_4-phthalimide	mesitylene-CH_2Cl_2-MeOH	5	40	89	**95** (*S*)[c]

[a]Molar ratio: $[Ir(cod)Cl]_2$/Ligand/Additive/Substrate=1/2.4/4/200; 100 atm (H_2). [b]Conversion was determined by GC. [c]Ee was determined by HPLC (Chiralpack AS) after *N*-acetylation with Ac_2O. The absolute configuration was determined by the sign of the specific rotation [lit.,[8] (1*S*)-(-)-1,2,3,4-tetrahydroharman (**2**): $[\alpha]_D^{25}$ –52° (*c* 2.0 EtOH); lit.,[9] (1*S*)-(-)-1,2,3,4-tetrahydroharmine (**4**): $[\alpha]_D^{rt}$ –58.6° (*c* 0.80 $CHCl_3$)].

In the absence of an additive, the enantioselectivity with BINAP was also low (Entry 4). When phthalimide was used as an additive in a mixed solvent of mesitylene, dichloromethane, and methanol, the enantioselectivity was considerably improved to 70% ee (Entry 5). 3,4,5,6-Tetrafluorophthalimide

was found to be a more efficient additive in increasing the enantioselectivity to 82% ee (Entry 6). Next, the asymmetric hydrogenation of a methoxy analog, 3,4-dihydroharmine (harmaline) (**3**), was carried out for obtaining optically active tetrahydroharmine (**4**). Using BCPM in the presence of tetrafluorophthalimide, the reaction proceeded smoothly but the enantioselectivity was moderate (Entry 7). BINAP was found to be a more efficient ligand even in the absence of phthalimide (Entry 8). The enantioselctivity of (*S*)-BINAP was also improved by phthalimide (from 62 to 72% ee) (Entry 9 vs 8), and in the presence of tetrafluorophthalimide the highest selectivity of 95% ee (*S*) was achieved (Entry 10). The natural 1,2,3,4-tetrahydroharmine is known to be an antipode, (*R*)-(+)-enantiomer,[9] which is also obtainable by using an antipode ligand, (*R*)-BINAP. The enantioselectivity of 95% ee is the best result reported so far for Ir-catalyzed asymmetric hydrogenation of 3,4-dihydro-1-methyl-β-carbolines.



We previously reported the correlation between the chirality of bidentate ligands and the absolute configuration of the products obtained by rhodium-catalyzed asymmetric hydrogenation or palladium-catalyzed asymmetric allylic alkylation. We first proposed a *P*/*M* chirality concept, [10] where the positioning array of four phenyl rings of diphosphine ligands closely correlates with the absolute configuration of products in asymmetric hydrogenations, and later represented a more general concept, *Pr*/*Mr* chirality[11] for classifying all chiral bidentate ligands. The ligands (*S*)-BINAP and (2*S*,4*S*)-BCPM, which are classified as possessing *Mr*-chirality, were revealed to show high *S*-selectivity in the Ir-catalyzed hydrogenation of 1-alkyl-3,4-dihydroisoquinolines[5] and 3,4-dihydro-1-methyl-β-carbolines.

In summary, we disclosed that a catalyst system of BINAP-Ir(I)-tetrafluorophthalimide showed very high enantioselectivity of up to 95% ee in the hydrogenation of 3,4-dihydro-β-carbolines. Further improvement of the catalyst system in terms of catalytic activity and enantioselectivity may be achieved by employing modified BINAP analogs.

EXPERIMENTAL

Asymmetric Hydrogenation of 3,4-Dihydro-1-methyl-β-carbolines: Typical Procedure

A solution of an iridium(I) complex catalyst was prepared *in situ* by mixing chloro(1,5-cycooctadiene)iridium(I) dimer (0.8 mg, 1.2 μmol) and (*S*)-BINAP (1.9 mg, 3 μmol) in degassed mesitylene (4 mL) was stirred at rt for 0.5 h under an argon atmosphere. In a glass tube containing a magnetic stirring bar were placed a solution of 3,4-dihydroharmine (**3**) (54 mg, 0.25 mmol) and 3,4,5,6-

tetrafluorophthalimide (1.1 mg, 5 μmol) in a mixed solvent (8 mL) of degassed methanol and dichloromethane (1:1), and a solution of the iridium(I) complex catalyst prepared above. The glass tube was placed in a stainless steel autoclave, and after ventilation with hydrogen (3 times) the pressure of hydrogen in the autoclave was adjusted at 100 atm. The mixture was stirred at 5 °C for 40 h. After ejection of the pressurized hydrogen, the reaction solution was treated with active charcoal and filtered. The conversion rate of the substrate was measured by GC (column: BPX 35). The structure of the hydrogenation product was confirmed by comparing the ^{1}H-NMR spectrum with an authentic one.[12] The ee value of the product was determined by HPLC after conversion of a small portion to its *N*-acetyl derivative[12] (column: Chiralpack AS; eluent: hexane/isopropyl alcohol=10/1 or 20/1, 1 mL/min; detection: 235 nm light); a derivative of 1,2,3,4-tetrahydroharmine (**4**) (eluent: 10/1): t_R=36.0 min, t_S=50.5 min; a derivative of 1,2,3,4-tetrahydroharman (**2**) (eluent: 20/1): t_R=50.0 min, t_S=67.0 min. All the results on asymmetric hydrogenation are summarized in Table 1.

REFERENCES

1. R. B. Herbert, 'The Chemistry and Biology of Isoquinoline Alkaloids,' ed. by J. D. Philipson, M. F. Roberts, and M. H. Zenk, Springer Verlag, Berlin, Heidelberg, New York, Tokyo, 1985, p. 213 ff.; M. Shamma, 'Isoquinoline Alkaloids, Chemistry and Pharmacology,' Academic Press, New York, 1972 ; T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Elsevier, Amsterdam, 1969.
2. M. D. Rozwadowska, *Heterocycles*, 1994, **39**, 903.
3. M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, and R. Noyori, *J. Org. Chem.*, 1994, **59**, 297.
4. C. A. Willoughby and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 11703.
5. T. Morimoto and K. Achiwa, *Tetrahedron: Asymmetry,* 1995, **6**, 2661; T. Morimoto, N. Suzuki, and K. Achiwa, *Heterocycles*, 1996, **43**, 2557.
6. N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916.
7. T. Morimoto, N. Nakajima, and K. Achiwa, *Chem. Pharm. Bull.*, 1994, **42**, 1951; T. Morimoto, N. Nakajima, and K. Achiwa, *Tetrahedron: Asymmetry,* 1995, **6**, 75; T. Morimoto, N. Nakajima, and K. Achiwa, *Synlett*, 1995, 748; T. Morimoto, N. Suzuki, and K. Achiwa, *Tetrahedron: Asymmetry,* 1998, **9**, 183.
8. H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 2614.
9. B. Schönenberger and A. Brossi, *Helv. Chim. Acta*, 1986, **69**, 1486; L. A. Chrisey and A. Brossi, *Heterocycles*, 1990, **30**, 267.
10. S. Sakuraba, T. Morimoto, and K. Achiwa, *Tetrahedron: Asymmetry,* 1991, **2**, 597.
11. A. Saitoh, K. Achiwa, K. Tanaka, and T. Morimoto, *J. Org. Chem.*, 2000, **65**, 4227.
12. S. Faizi and A. Naz, *Tetrahedron*, 2002, **58**, 6185.