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An Improved Diphosphine-Iridium(I) Catalyst System for the Asymmetric Hydrogenation of Cyclic Imines: Phthalimide as an Efficient Co-catalyst[1]

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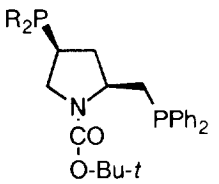
Abstract: The asymmetric hydrogenation of cyclic ketimines, 1-alkyl-3,4-dihydroisoquinolines **5a,b**, was carried out with diphosphine-iridium(I) complex catalysts in the presence of various imides or amides as a co-catalyst. Remarkable effects of five-membered imides on the enantioselectivity and the catalytic activity were observed. The enantioselectivity with a BCPM 1-iridium(I) complex was much improved up to 93% ee by addition of phthalimide.

While extensive efforts have led to successful methods for the enantioselective hydrogenation of olefins and ketones,[2] much less work has been reported for the enantioselective conversion of prochiral imines to chiral amines with transition metal catalysts.[3-7] Among them, rhodium or iridium complexes of chiral diphosphines, Cycphos,[4] Duphos,[5] BDPP,[6] and sulfonated BDPP,[7] have been reported as efficient catalysts for the asymmetric hydrogenation of ketimines most of which bear acyclic *E*-forms. In the majority of these Rh(I), Ir(I), and Ir(III) complex systems, an iodide (or an iodine component) was found to be indispensable as a co-catalyst for improving the enantioselectivity and the catalytic activity.[4,6]

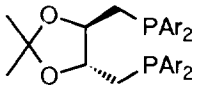
We have recently reported that the catalyst systems of Ir(I)-MOD-DIOP **3**-tetrabutylammonium iodide[8] and Ir(I)-BCPM **1**-bismuth(III) iodide[9] are efficient for the asymmetric hydrogenation of a cyclic ketimine, 2,3,3-trimethylindolenine, and a high enantiomeric excess of up to 91% ee has been attained. However, six-membered imines, 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **5a**[10] and 1-alkyl-3,4-dihydro-β-carbolines, could not be hydrogenated in high ee by using these catalyst systems.

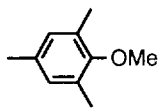
It is well-known that the enantioselective reductions of ketones[11] or imines which lack hetero-functional groups anchoring transition metals are generally more difficult than the hydrogenations of the hetero-functionalized ketones or imines,[5] and neutral metal (Rh(I) or Ir(I)) complexes usually show higher enantioselectivity than the cationic ones. On the other hand some prochiral ketimines were hydrogenated in high enantioselectivity, as mentioned above, with neutral rhodium or iridium complexes in the presence of an iodide.[4,6,8,9] These facts imply that the selection of suitable halides or other additives which can coordinate to the vacant site of the diphosphine-rhodium or -iridium complex (forming a neutral complex) is important for the improvement of the enantioselectivity in the hydrogenation of ketones or imines bearing no α- or β-hetero-functional groups. We then planned to use other additives in place of iodides in order to improve the enantioselectivity in the hydrogenation of six-membered imines (*Z*-forms). The extensive search for the efficient co-catalysts suggested that imides[12] have effects on the improvement of both the enantioselectivity and the catalytic activity of the diphosphine-iridium(I) complex. We now report an efficient procedure for the catalytic asymmetric hydrogenation of six-membered imines **5a,b** employing a BCPM **1**-Ir(I)-imide system.



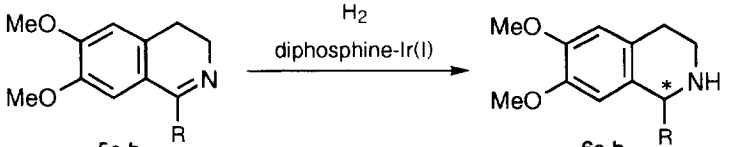
(2*S*,4*S*)-BCPM **1**: R = *c*-C_6H_{11}

(2*S*,4*S*)-BPPM **2**: R = Ph



(4*R*,5*R*)-MOD-DIOP **3**: Ar = 

(4*R*,5*R*)-DIOP **4**: Ar = Ph



5a,b

a: R = Me
b: R = Et

6a,b

In general, the asymmetric hydrogenation of **5a** was carried out under an initial hydrogen pressure of 100 atm with 1 mol% of Ir(I) complex catalyst prepared *in situ* from (2*S*,4*S*)-BCPM **1**, $[Ir(COD)Cl]_2$, and a co-catalyst of imide or amide {molar ratio; imine : diphosphine : $[Ir(COD)Cl]_2$: co-catalyst = 200 : 2.4 : 1 : 4} in various solvents. The results are summarized in Table 1.[13] When no additive was present or an iodide such as bismuth(III) iodide or tetrabutylammonium iodide was added as a co-catalyst, the enantioselectivities were lower than 20% ee (entries 1-4). When various five-membered imides such as succinimide, hydantoin, phthalimides, and 2,3-naphthalenecarboximide, were used as the co-catalyst, the enantioselectivities were remarkably improved (entries 5-22) and the catalytic activity was much increased with phthalimide (entries 2,14). A larger amount of phthalimide (/Ir=10) had no effect on changing the selectivity (entries 9,10). Clear effects of solvents on the enantioselectivity were observed; less polar solvents showed higher selectivities (entries 7,8,11,12,15-21). The effects on the enantioselectivity of changing the substituents of phthalimide or the hydrogen pressure were small (entries 18-21 and entries 12,14). Considerable effects of temperature on the enantioselectivity were observed especially in use of a protic solvent such as benzene-methanol; lower temperatures showed better selectivities (entries 8,9,12,13). Amides, saccharin, and six-membered imides showed almost no effects on the enantioselectivity (entries 23-28). When other diphosphine ligands, BPPM **2**, DIOP **4**, and MOD-DIOP **3** were used, their enantioselectivities were lower than that with BCPM **1** (entries 29-34). Among them a MOD-DIOP **3**-Ir(I)-phthalimide system showed the best selectivity at a low temperature in benzene-methanol (entry 33). Thus the asymmetric hydrogenation of **5a** catalyzed by an iridium(I) complex of (2*S*,4*S*)-BCPM **1** in the presence of phthalimide as a co-catalyst gave (*S*)-salsolidine **6a** in up to 93% ee. Asymmetric hydrogenation of an ethyl analog **5b** was also carried out under similar conditions affording **6b** in 79% ee.

It is noted that the five-membered imides have remarkable effects on the improvement of the enantioselectivities of the modified diphosphine-iridium(I) complex catalysts and this is the first efficient procedure for the catalytic asymmetric hydrogenation of 1-alkyl-3,4-dihydroisoquinolines with diphosphine-transition metal complex catalysts. These findings will provide a strategy for the development of other efficient

Table 1. Asymmetric Hydrogenation of 3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline **5a**[a]

Entry	Ligand	Additive	Solvent	Temp. (°C)	Time (h)	Convn. (%)	E.e. (%)
1	(2*S*,4*S*)-BCPM **1**	none	benzene-MeOH	20	24	90	18 (*R*)
2	"	"	toluene	"[b]	"	22	14 (*S*)
3	"	BiI_3 (/Ir=2/3)	benzene-MeOH	"	48	92	12 (*S*)
4	"	Bu_4N·I	"	"	50	97	10 (*S*)
5	"	succinimide	"	-10	72	94	67 (*S*)
6	"	hydantoin	"	20	30	96	49 (*S*)
7	"	phthalimide	MeOH	"	24	97	43 (*S*)
8	"	"	benzene-MeOH	"	30	96	44 (*S*)
9	"	"	"	-10	48	98	**76** (*S*)
10	"	" (/Ir=10)	"	"	"	94	**76** (*S*)
11	"	"	benzene	20	24	96	**70** (*S*)
12	"	"	toluene	"	"	94	**79** (*S*)
13	"	"	"	2-5	"	95	**85~93** (*S*)
14	"	"	"	20[b]	"	82	**75** (*S*)
15	"	"	THF	20	20	95	41 (*S*)
16	"	"	CH_2Cl_2	"	"	94	**70** (*S*)
17	"	"	*p*-xylene	"	"	95	**78** (*S*)
18	"	4-Cl-phthalimide	benzene-MeOH	"	30	95	56 (*S*)
19	"	"	toluene	"	20	97	**81** (*S*)
20	"	4,5-Cl_2-phthalimide	benzene-MeOH	"	24	95	53 (*S*)
21	"	"	toluene	"	20	95	**76** (*S*)
22	"	2,3-naphthalenecarboximide	"	"	"	96	**74** (*S*)
23	"	1,8-naphthalimide	benzene-MeOH	"	45	66	3 (*R*)
24	"	glutarimide	"	"	30	81	3 (*R*)
25	"	saccharin	"	"	45	82	4 (*R*)
26	"	benzamide	"	"	48	88	14 (*R*)
27	"	formamide (/Ir=70)	"	"	"	37	25 (*R*)
28	"	2-pyrrolidone (/Ir=8)	"	"	"	85	12 (*R*)
29	(2*S*,4*S*)-BPPM **2**	Bu_4N·I	"	"	90	100	7 (*S*)
30	"	phthalimide	toluene	"	20	87	7 (*S*)
31	(4*R*,5*R*)-DIOP **4**	"	"	"	"	52	26 (*S*)
32	(4*R*,5*R*)-MOD-DIOP **3**	"	"	"	"	78	32 (*S*)
33	"	"	benzene-MeOH	-10	60	51	68 (*S*)
34	"	Bu_4N·I	"	20	90	91	28 (*S*)

[a] Ligand : $[Ir(COD)Cl]_2$: Additive : **5a** = 2.4 : 1 : 4 : 200; 100 atm (H_2). [b] 20 atm (H_2).

catalyst systems. Further improvement of the catalyst system and application to the synthesis of other optically active isoquinoline alkaloids and related compounds are in progress.

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8. Morimoto, T. Nakajima, N.; Achiwa, K. *Chem. Pharm. Bull.* **1994**, *42*, 1951.
9. Morimoto, T. Nakajima, N.; Achiwa, K. *Synlett* **1995**, in press.
10. Few reports on the catalytic asymmetric hydrogenation of 1-alkyl-3,4-dihydroisoquinolines have appeared: hydrogenation using chiral titanocene (ref. 3); hydrosilylation using DIOP-Rh (Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353.); non-reducible with Cycphos-Rh (ref. 4), although several types of reductions using a stoichiometric amount of chiral reagents have been reported: reduction with triacyloxyborohydride (Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc. Perkin Trans. 1* **1983**, 265.); reduction with oxaborolidines (Nakagawa, M.; Kawata, T.; Kakikawa, T.; Yamada, H.; Matsui, T.; Hino, T. *Tetrahedron* **1993**, *49*, 1739). An alternative method for the catalytic asymmetric synthesis of isoquinoline alkaloids has been developed by employing asymmetric hydrogenations of cyclic enamides (Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117; Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297; Morimoto, T. Nakajima, N.; Achiwa, K. *Tetrahedron Asymmetry* **1995**, *6*, 75.).
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12. Colquhoun and co-workers reported previously that a succinimide- (or phthalimide-) derived ligand in transition metal complexes is regarded as neutral and closely resembles a halogen (strong σ-acceptor and moderate π-donor), and several diphosphine-transition metal-imide complexes were isolated and identified (Adams, H.; Bailey, A.; Briggs, T. N.; McCleverty, A.; Colquhoun, H. M.; Williams, D. J. *J. Chem. Soc. Dalton Trans.* **1986**, 813.).
13. A typical procedure for the asymmetric hydrogenation of **5a** is as follows: A mixture of chloro(1,5-cyclooctadiene)iridium(I) dimer, $[Ir(COD)Cl]_2$ (1.6 mg, 2.5 x 10^{-3} mmol), (2*S*,4*S*)-BCPM **1** (3.4 mg, 6.0 x 10^{-3} mmol) in a degassed solvent (3.0 ml) was stirred for 15 min under an argon atmosphere to form a clear solution. The catalyst solution was added to a mixture of **5a** (103 mg, 0.50 mmol) and phthalimide 1.5 mg, 1x10^{-2} mmol) in a glass tube. The glass tube was placed in an autoclave (100 ml), pressurized with hydrogen to 100 atm after several exchange with hydrogen, and stirred under the conditions (temp. and time) shown in Table 1. Conversion was determined by GLC (a capillary column: BPX 35) and ee was measured, after conversion of the product **6a** to the corresponding *N*-acetyl derivative, by HPLC (a chiral stationary column: Chiralpack AS) using a mixed solvent of hexane-isopropyl alcohol (20:1). The absolute configuration of **6a** was determined by comparison of the optical rotation with that reported for optically pure (*S*)-**6a**: $[\alpha]_D^{22}$ -59.5 (*c* 4.39, EtOH) (Battersby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214.).

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