ASYMMETRIC SYNTHESIS OF (*S*)-NORLAUDANOSINE AND (*S*)-TETRAHYDROHOMOPAPAVERINE BY CATALYTIC ASYMMETRIC HYDROGENATION WITH CHIRAL DIPHOSPHINE-IRIDIUM(I)-PHTHALIMIDE COMPLEX CATALYSTS[1]

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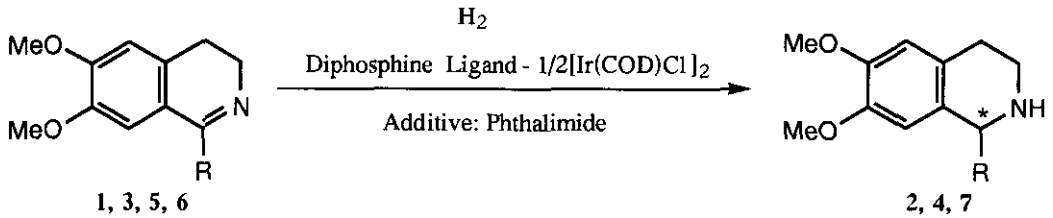
Abstract —— Optically active 1,2,3,4-tetrahydroisoquinoline alkaloids, (*S*)-norlaudanosine and (*S*)-tetrahydrohomopapaverine, were prepared by catalytic asymmetric hydrogenation of 1-substituted 3,4-dihydro-6,7-dimethoxyisoquinolines with 1 mol % of an iridium(I) complex of (2*S*,4*S*)-BCPM or (*S*)-BINAP in the presence of a phthalimide. Enantioselectivities of up to 88% ee were attained.

A group of 1-substituted 1,2,3,4-tetrahydroisoquinolines, among which 1-benzyl derivatives are the most widely distributed, is one of the most important alkaloids since they have marked physiological activities and serve as synthetic precursors in other types of alkaloids such as aporphines and morphines.[2] Most of the isoquinoline alkaloids isolated from many kinds of plants have enantiomerically pure forms bearing 1-*S* configuration. Although numerous works on the asymmetric synthesis of optically active isoquinoline alkaloids have been explored,[3] most of them are based on the procedures employing a stoichiometric amount of chiral building blocks, auxiliaries, or reagents. Very few methods for their catalytic asymmetric synthesis have been reported; for example, asymmetric reduction of 3,4-dihydroisoquinolines by hydrogenation using a chiral titanocene catalyst,[4] by transfer hydrogenation with formic acid using chiral *N*-sulfonated diamine Ru catalysts,[5] or by hydrosilylation using a DIOP-Rh catalyst,[6] and asymmetric hydrogenation of enamides using a BINAP-Ru catalyst.[7]

We have recently found that addition of tetrabutylammonium iodide,[8] bismuth(III) iodide,[9] or five-membered imides[10] to a complex of MOD-DIOP-Ir(I) or BCPM-Ir(I) can improve the enantioselectivity of asymmetric hydrogenation of cyclic imines and a complex of BCPM-Ir(I)-phthalimide is an efficient catalyst for asymmetric hydrogenation of a 3,4-dihydro-1-methylisoquinoline. We report herein



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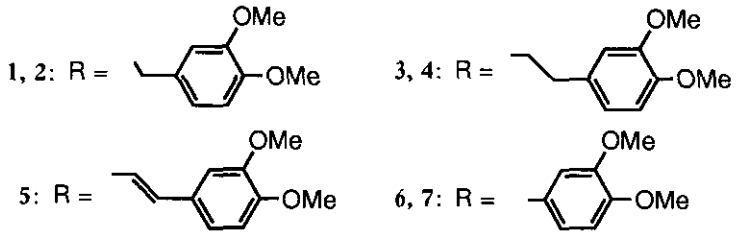
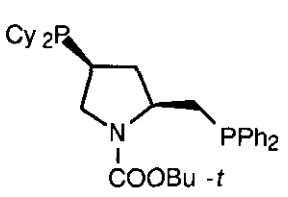
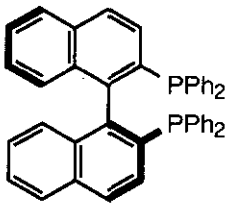




(2*S*,4*S*)-BCPM (8)



(*S*)-BINAP (9)

asymmetric hydrogenation of 1-arylmethyl-, 1-(2-arylethyl)-, 1-(2-arylvinyl)-, and 1-aryl-substituted 3,4-dihydro-6,7-dimethoxy-isoquinolines (**1**, **3**, **5**, and **6**) with iridium(I) complexes of (2*S*,4*S*)-BCPM (**8**) and (*S*)-BINAP (**9**) in the presence of phthalimides, leading to optically active norlaudanosine (**2**), tetrahydrohomopapaverine (**4**), and cryptostyline II (**7**).

Asymmetric hydrogenation of 3,4-dihydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (**1**) was carried out at 2-5 °C under an initial hydrogen pressure of 100 atm with 1 mol% of an Ir(I) complex catalyst prepared *in situ* from (2*S*,4*S*)-BCPM (**8**), $[Ir(COD)Cl]_2$, and phthalimide (used as a co-catalyst) in a molar ratio of 2.4:1:4 in toluene. The reaction proceeded almost completely in 20 h affording the corresponding hydrogenation product, (*S*)-norlaudanosine (**2**), the enantiomeric excess of which was determined to be 72% ee by hplc with a chiral stationary phase column, Chiralpack AS, after conversion to its *N*-acetyl derivative (Entry 1 in Table 1). In the absence of phthalimide the enantioselectivity was much lower and the catalytic activity was low (Entry 2). When 3,4,5,6-tetrafluorophthalimide was used at a lower temperature, somewhat better selectivity (88% ee) was obtained (Entry 3). We found that among several diphosphine ligands, (*S*)-BINAP (**9**) is also effective in this Ir(I) catalyst system using a

Table 1. Asymmetric Hydrogenation of 1-Substituted 3,4-Dihydro-6,7-dimethoxyisoquinolines (**1**,**3**,**5**,**6**)[a]

Entry	Substrate	Ligand	Additive	Temp. (°C)	Time (h)	Convn.[b] (%)	E.e.[c] (%)
1	**1**	(2*S*,4*S*)-BCPM (**8**)	phthalimide	23	20	88	**72** (*S*)
2	**1**	"	none	"	"	30	27 (*S*)
3	**1**	"	F_4-phthalimide	5	"	84	**88** (*S*)
4	**1**	(*S*)-BINAP (**9**)	phthalimide	"	"	67	**84** (*S*)
5	**1**	"	none	"	"	18	35 (*S*)
6	**3**	(2*S*,4*S*)-BCPM (**8**)	phthalimide	2	22	75	**87** (*S*)
7	**3**	"	F_4-phthalimide	"	"	98	**81** (*S*)
8	**3**	"	none	"	"	6	----
9	**3**	(*S*)-BINAP (**9**)	phthalimide	"	40	89	**82** (*S*)
10	**3**	"	F_4-phthalimide	"	"	89	**86** (*S*)
11	**5**	(2*S*,4*S*)-BCPM (**8**)	phthalimide	"	24	79	**86** (*S*)
12	**5**	"	F_4-phthalimide	"	"	87	**83** (*S*)
13	**6**	(*S*)-BINAP (**9**)[d]	phthalimide	5	96	50	31 (*R*)[e]

[a] Molar ratio; substrate : ligand : $[Ir(COD)Cl]_2$: phthalimide = 200:2.4:1:4. Hydrogen pressure; 100 atm. Solvent; toluene (for ligand **8**) or toluene-MeOH (for ligand **9**). [b] Determined by glc analysis or hplc analysis. [c] Determined by hplc analysis with a chiral stationary phase column, Chiralcel OD-H, or with a column, Chiralpack AS, after conversion of the products to their *N*-acetyl derivatives. The absolute configurations were determined by comparison of the optical rotation values with those reported [(*R*)-norlaudanosine (*R*-**2**): $[\alpha]_D^{20}$ +32.1 (*c* 1.528, $CHCl_3$) (ref. 11); (*S*)-norhomolaudanosine (*S*-**4**): $[\alpha]_D^{21}$ -17.7 (*c* 0.23, EtOH) (ref. 12)]. [d] Substrate : Ir complex catalyst = 50:1. [e] The absolute configuration was determined by comparison of its retention time on hplc (Chiralcel OD-H) with that of an authentic specimen (*S*-**7**) prepared by a reported procedure (ref. 13).

phthalimide as a co-catalyst (Entry 4). In the BINAP (**9**)-Ir(I)-phthalimide system, however, the reaction must be carried out in toluene-methanol to gain high enantioselectivity and catalytic activity. In the hydrogenation of **1** using the complex catalysts of **8** or **9**, unexpected results were obtained occasionally; a considerable amount of a dehydrogenated product, papaverine, was produced under the same conditions. Asymmetric hydrogenation of 1-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (**3**) was also carried out in similar conditions employing a (2*S*,4*S*)-BCPM (**8**)- or (*S*)-BINAP (**9**)-Ir(I)-phthalimide system. The results in Table 1 show that the iridium(I) complexes of BCPM (**8**) and

BINAP (**9**) have high enantioselectivity in the presence of phthalimides affording (*S*)-tetrahydrohomopapaverine (**4**) in up to 87% ee (Entries 6-10). A styryl analog (**5**) was also hydrogenated with the complex catalysts of (2*S*,4*S*)-BCPM (**8**) and similar results were obtained (Entries 11, 12). On the other hand, asymmetric hydrogenation of 1-(3,4-dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxy-isoquinoline (**6**) hardly proceeded under similar conditions; for example, using (*S*)-BINAP (**9**)-Ir(I)-phthalimide (or none) (96-116 h) the conversion was below 15% (in use of 2 mol% of the catalyst, the conversion was 50%) and the enantioselectivity of the product, cryptostyline II (**7**), was low (31-33% ee (*R*)).

In conclusion, the catalyst systems of BCPM (**8**)- and BINAP (**9**)-Ir(I)-phthalimide are very efficient in asymmetric hydrogenation of 1-arylmethyl- and 1-(2-arylethyl)- or 1-styryl-3,4-dihydroisoquinolines, and the present study will provide a general and useful method for the preparation of optically pure isoquinoline alkaloids such as 1-substituted tetrahydroisoquinolines and their derivatives.

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