SYNTHESIS OF AXIALLY DISSYMMETRIC BIPHENYLBISPHOSPHINE LIGANDS, BIMOPS AND ASYMMETRIC HYDROGENATIONS OF β-KETO ESTER AND α,β-UNSATURATED CARBOXYLIC ACID CATALYZED BY THEIR RUTHENIUM (II) COMPLEXES[1)]

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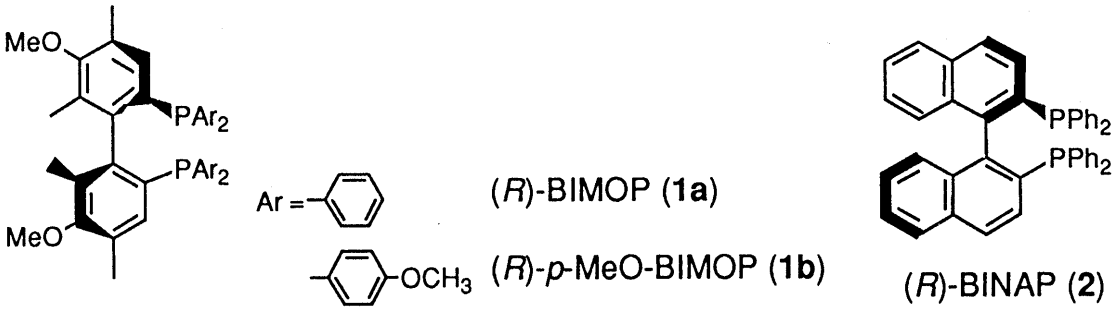
Axially dissymmetric biphenylbisphosphine ligands, BIMOP (**1a**) and *p*-MeO-BIMOP (**1b**) have been newly designed and prepared. The ruthenium (II) complexes of (*R*)-**1a** and **1b** proved to be excellent catalysts in asymmetric hydrogenations of methyl 3-oxobutanoate and tiglic acid affording (*R*)-methyl 3-hydroxybutanoate of 95-99 % ee and (*R*)-2-methylbutyric acid of 86-91 % ee, respectively.

KEYWORDS chiral bisphosphine ligand; axially dissymmetric biphenylbisphosphine; ruthenium (II) complex; catalyst; asymmetric hydrogenation; β-keto ester; α,β-unsaturated carboxylic acid

To date, many chiral bisphosphine ligands for rhodium (I)-catalyzed asymmetric hydrogenation have been developed, and some of them showed almost complete enantioselectivity in the hydrogenations of *N*-acyldehydroamino acids. Recently, it has been found that BINAP (**2**) could be utilized also for the ruthenium (II)-catalyzed system.[2)] The BINAP (**2**)-ruthenium (II) complex is an unparalleled highly efficient catalyst in asymmetric hydrogenations of various olefins and ketones, although most of the hydrogenations needed to be carried out under conditions of relatively higher pressures and temperatures. On the other hand, the ruthenium (II) complexes of other chiral bisphosphines do not work well as the catalyst in those reactions.

BINAP (**2**) has a binaphthyl moiety, and its asymmetric source is derived from the carbon (1)-carbon (1') axiality. The steric and electronic characteristics based on its skeleton are remarkably different from those of other chiral bisphosphine ligands. We anticipated that it was necessary to possess an axially dissymmetric biaryl skeleton for the ligand which was successfully applicable for both rhodium (I)- and ruthenium (II)-catalyzed asymmetric hydrogenations. Moreover, we expected that it was also necessary to introduce electron donating substituents such as methoxy and methyl groups into the biaryl moiety in order to increase the catalytic efficiency of both its rhodium (I) complex and ruthenium (II) complex under mild reaction conditions. In the previous communications, we reported BPPM and DIOP analogues, MOD-BPPM [3)] and MOD-DIOP [4)] bearing 4-methoxy and 3,5-dimethyl groups on each phenyl group, and their rhodium (I) complexes were excellent catalysts which exhibited much higher catalytic activities and enantioselectivities in asymmetric hydrogenations of *N*-acyldehydroamino acids and itaconic acids than the complexes of BPPM and DIOP. These results were considered to be caused by the electronic effects of both 4-methoxy and 3,5-dimethyl groups and the steric effects of 3,5-dimethyl groups.

In this communication, we describe the preparation of 6,6'-bis(diphenylphosphino)-3,3'-dimethoxy-2,2',4,4'-tetramethyl-1,1'-biphenyl (**1a**) (abbreviated to BIMOP) and its derivative (**1b**) (abbreviated to *p*-MeO-BIMOP), and the asymmetric hydrogenation of β-keto ester and α,β-unsaturated carboxylic acid catalyzed by the ruthenium (II) complexes of optically pure **1a** and **1b**.



Optically pure BIMOPs (**1a** and **1b**) were synthesized by a procedure shown in Chart 1. Starting from iodination of 2,6-dimethylnitrobenzene, a methoxy group was introduced in good yield by reduction of the nitro group followed by diazotization of the resulting amino group, and methanolysis. Compound **5** was converted to the coupling product (**6**) by Ullmann reaction, and then bromination of **6** afforded the racemic dibromide (**7**). After dilithiation of **7** with *tert*-butyllithium in tetrahydrofuran at -70 °C, phosphination with diphenylphosphinyl chloride furnished BIMOPO (**8a**). *p*-MeO-BIMOPO (**8b**) was also obtained by treatment with chlorodi(4-methoxyphenyl)phosphine followed by oxidation of the phosphino groups. Optical resolution of the racemic **8a** and **8b** was achieved by using optically active (2*R*,3*R*)-(-)-2,3-O-dibenzoyltartaric acid as a resolving agent. The optical purity of the resolved **8a** and **8b** was determined to be 100% ee by HPLC analysis (Waters:Opti-Pak TP). Finally, the phosphinyl groups of optically active **8a** and **8b** were reduced by heating with trichlorosilane in the presence of triethylamine in chlorobenzene to yield the corresponding BIMOP (**1a**) [5] and *p*-MeO-BIMOP (**1b**) [6] without racemization. The absolute configuration of optically pure **1a** and **1b** was determined to be *R* by comparison of their CD spectra with that of (*R*)-(-)-BIPHEMP [7] whose absolute configuration was already determined by X-ray crystallography.

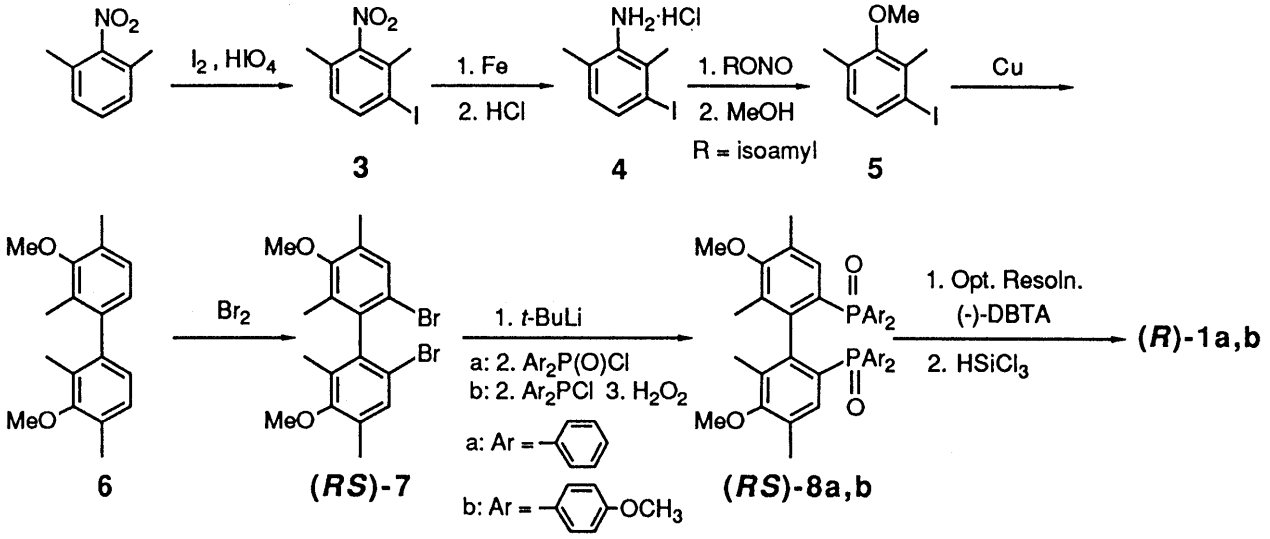
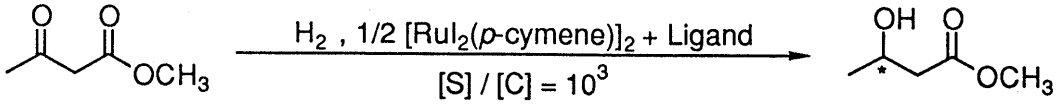


Chart 1

The ruthenium (II)-catalyzed asymmetric hydrogenation of ß-keto ester, methyl 3-oxobutanoate [8] was first chosen as a model reaction for evaluation of the capability of the newly synthesized ligands, BIMOPs (**1a** and **1b**) and for comparison with BINAP (**2**). The cationic ruthenium (II) complexes of (*R*)-**1a**, **1b**, and **2** were prepared just prior to use by mixing and heating ruthenium diiodide *p*-cymene complex and each ligand for 10 min in methanol-dichloromethane (1:1) under an argon atmosphere. All the reactions were carried out by using the substrate to the catalyst molar ratio (S/C) of 1000 at 30-40 °C for 20 h in methanol-dichloromethane (1:1) under an initial hydrogen pressure of 30 atm. The results are summarized in Table I. All the hydrogenations proceeded smoothly to give (*R*)-methyl 3-hydroxybutanoate in nearly quantitative yields. The (*R*)-BIMOP (**1a**)-ruthenium (II) complex showed extremely high (99% ee) enantioselectivity, and the (*R*)-*p*-MeO-BIMOP (**1b**)-ruthenium (II) complex was revealed to have superior chiral recognition ability as well, although slightly lower optical yields (95% ee) was obtained than using the ruthenium (II) complex of **1a** as the catalyst. Next, asymmetric hydrogenation of α,β-unsaturated carboxylic acid, tiglic acid [8b, 9] was carried out in a 0.5 M methanol-dichloromethane (4:1) solution of the substrate in the presence of the ruthenium (II) complex catalyst (0.1 mol%) at 50-60 °C for 24 h under an initial hydrogen pressure of 5 atm. As summarized in Table II, all the hydrogenations proceeded to completion, and both the complexes of **1a** and **1b** gave (*R*)-2-methylbutyric acid in nearly quantitative yields with high enantioselectivity (86-91% ee). Thus, BIMOPs (**1a** and **1b**) proved to be efficient ligands as well as BINAP (**2**) with respect to the enantioselectivity in the hydrogenations of methyl 3-oxobutanoate and tiglic acid.

Further investigaions along this line are in progress, and application to asymmetric hydrogenation catalyzed by their rhodium (I) complexes will be reported in the near future.

Table I. **Asymmetric Hydrogenation[a] of β-Keto Ester**

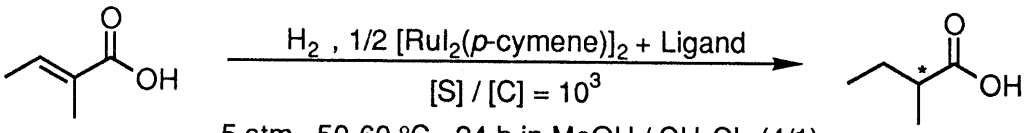


30 atm , 30-40 °C , 20 h in MeOH / CH_2Cl_2 (1/1)

Ligand	Convn.(%)[b]	e.e.(%)[c]	Confign.[d]
(*R*)-BINAP	100	98	*R*
(*R*)-BIMOP	100	99	*R*
(*R*)-*p*-MeO-BIMOP	100	95	*R*

a) All hydrogenations were carried out in 0.5 M solution of the substrate. b) Determined by GLC analysis. c) Determined by HPLC analysis on Chiralcel OB (Daicel) of the ester derived from the product and benzoyl chloride. d) Determined by the sign of optical rotation.

Table II. **Asymmetric Hydrogenation[a] of α,β-Unsaturated Carboxylic Acid**



5 atm , 50-60 °C , 24 h in MeOH / CH_2Cl_2 (4/1)

Ligand	Convn.(%)[b]	e.e.(%)[c]	Confign.[d]
(*R*)-BINAP	100	87	*R*
(*R*)-BIMOP	100	91	*R*
(*R*)-*p*-MeO-BIMOP	100	86	*R*

a) All hydrogenations were carried out in 0.5 M solution of the substrate. b) Determined by NMR analysis. c) Determined by HPLC analysis on Chiralcel OD (Daicel) of the amide derived from the product and (*S*)-1-(1-naphthyl)ethylamine. d) Determined by the sign of optical rotation.

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6) (*R*)-(-)-*p*-MeO-BIMOP: $[\alpha]_D$ -2.4 °, mp 276-277 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, s, CH_3), 2.22 (6H, s, CH_3), 3.51 (6H, s, OCH_3), 3.78 (12H, s, OCH_3), 6.77-6.82 (10H, m, arom.H), 7.12-7.21 (8H, m, arom.H).
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